American College of Physicians

Colorado Chapter
Feb 4th, 2016

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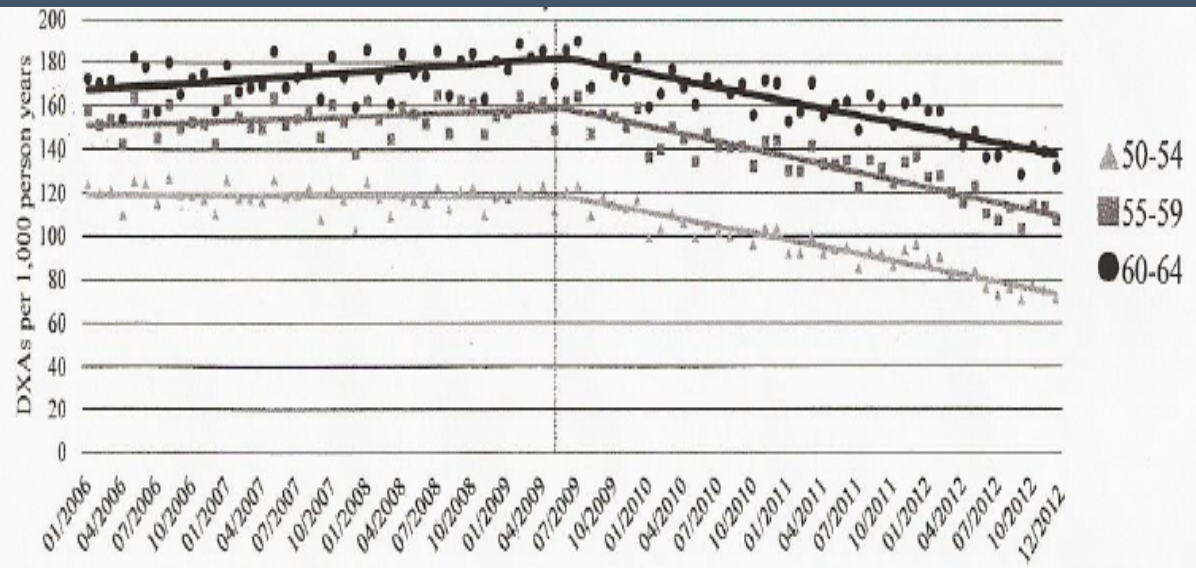
Disclosures

- 1. Research Grants: Alexion, Amgen, Lilly, Merck, Novartis, Radius Pharma, AgnoVos, Boehringer-Ingelheim, Regeneron, Takeda.
- 2. Scientific boards: Amgen, Lilly, Merck, Radius Health
- 3. Speakers bureaus: None
- 4. Equity: None

Update in Postmenopausal Osteoporosis

1. Underdiagnoses and under treatment-why?
2. Selection of the high risk patients
3. Drug Holidays
4. New therapies

Declining DXA Testing



2006	2007	2008	2009	2010	2011	2012	
119.7	118.1	117.8	117.9	103	92.8	79.3	**50-54**
152.3	153.3	155.6	157	141.5	132.3	115.1	**55-59**
169.9	172.5	176.1	179.7	167.5	159.2	142	**60-64**

Fig. 1. Dual energy X-ray absorptiometry utilization in women aged 50–64 yr per 1000 person years by month (2006–2012) with seasonal adjustment.

Forentino D et al. J Clin Densit 2015

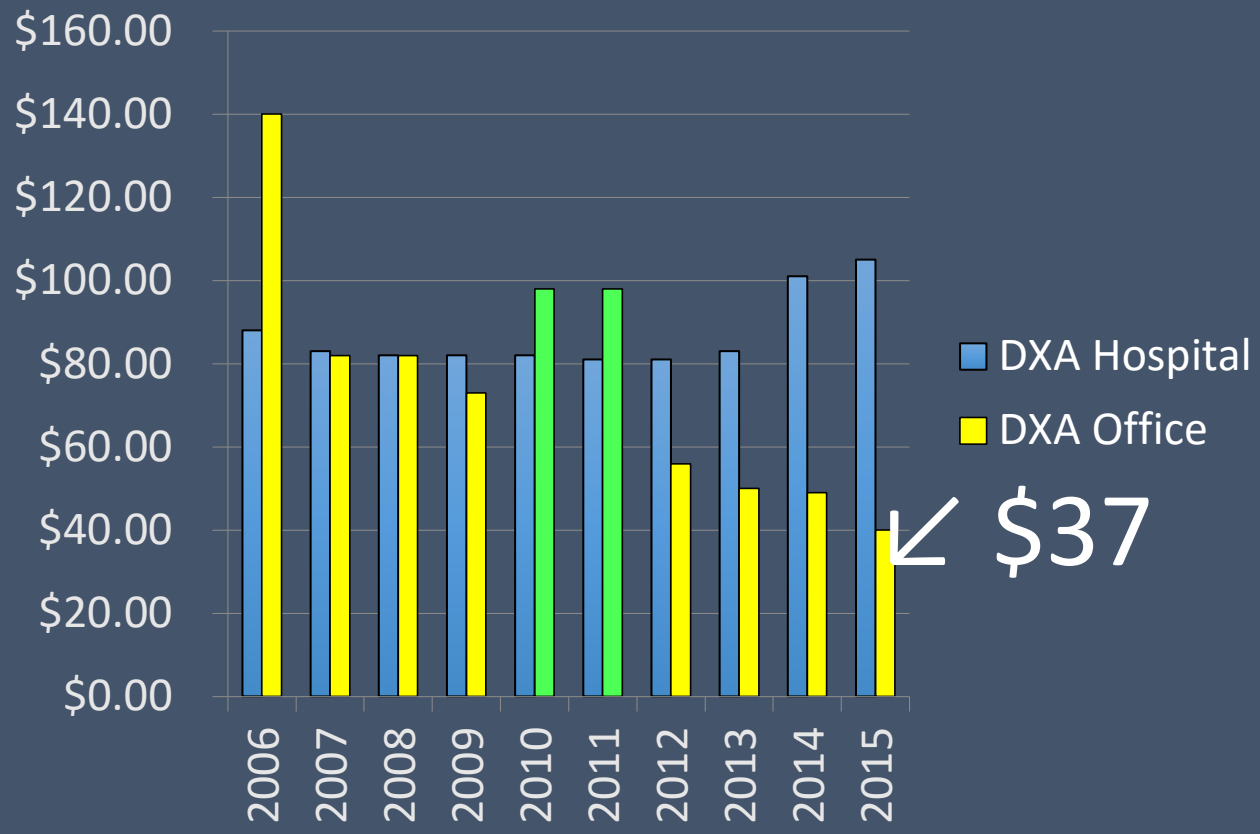
Access to DXA Testing is Declining in Colorado

- DXA testing of 65+ yo women in Colorado peaked in 2007, when Medicare started cutting DXA reimbursement.
- Since 2007, 28 DXA sites have stopped providing DXA in Colorado.
- Between 2009-2012, testing of women 65+ declined by 22% in Colorado.(despite USSG and USPSTF endorsing population screening)
- From 2009-2012, 14,551 fewer women had DXA tests that likely resulted in:
  - 122 additional hip fractures
  - 24 additional deaths
  - $4,889,286 in estimated additional costs to Medicare.

Forentino D et al ISCD 2015

Comparison of Medicare DXA Payment 2006-15: Hospital vs. Office

DXA Office Payment Dropped by 75% While Hospital rates Increased by 22%

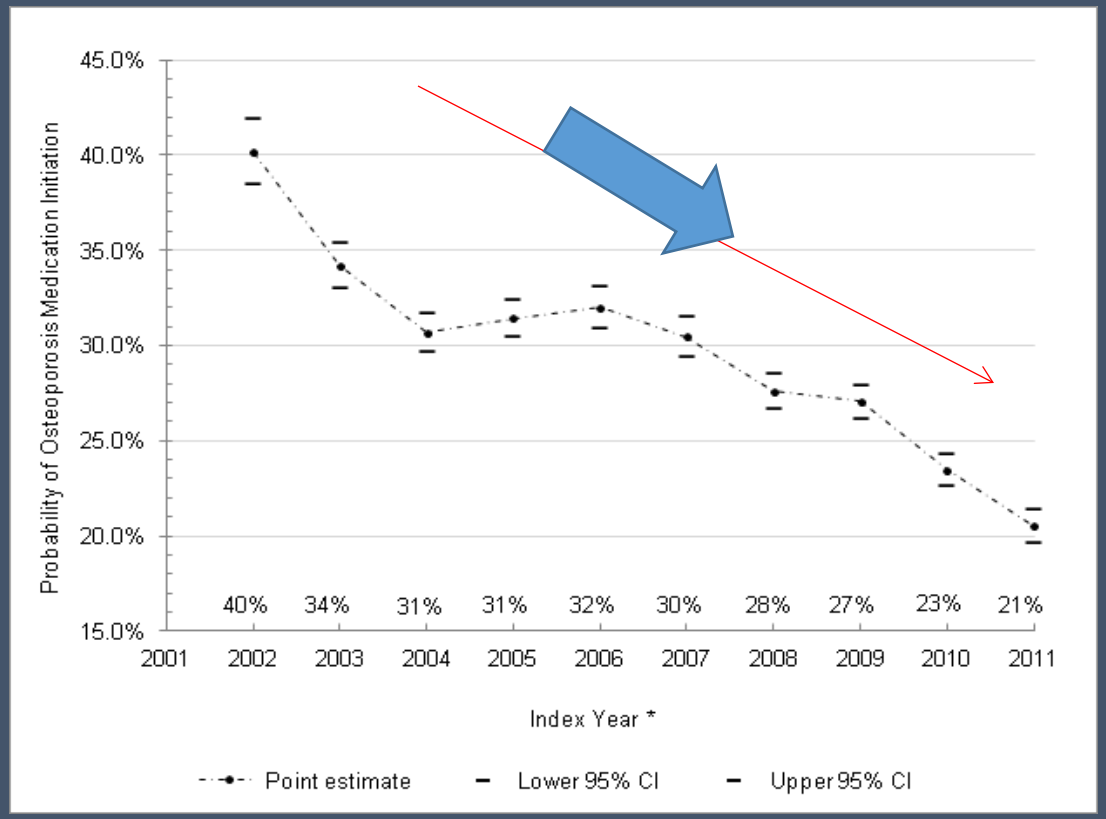


Breakeven $96

HR Bill 281 : National average $98

Forentino D et al ISCD 2014

Annual Unadjusted Probability of Osteoporosis Medication Use after Discharge from Hospital for Hip Fracture



Solomon D et al JBMR 2014

Annual Cost per Hospitalization

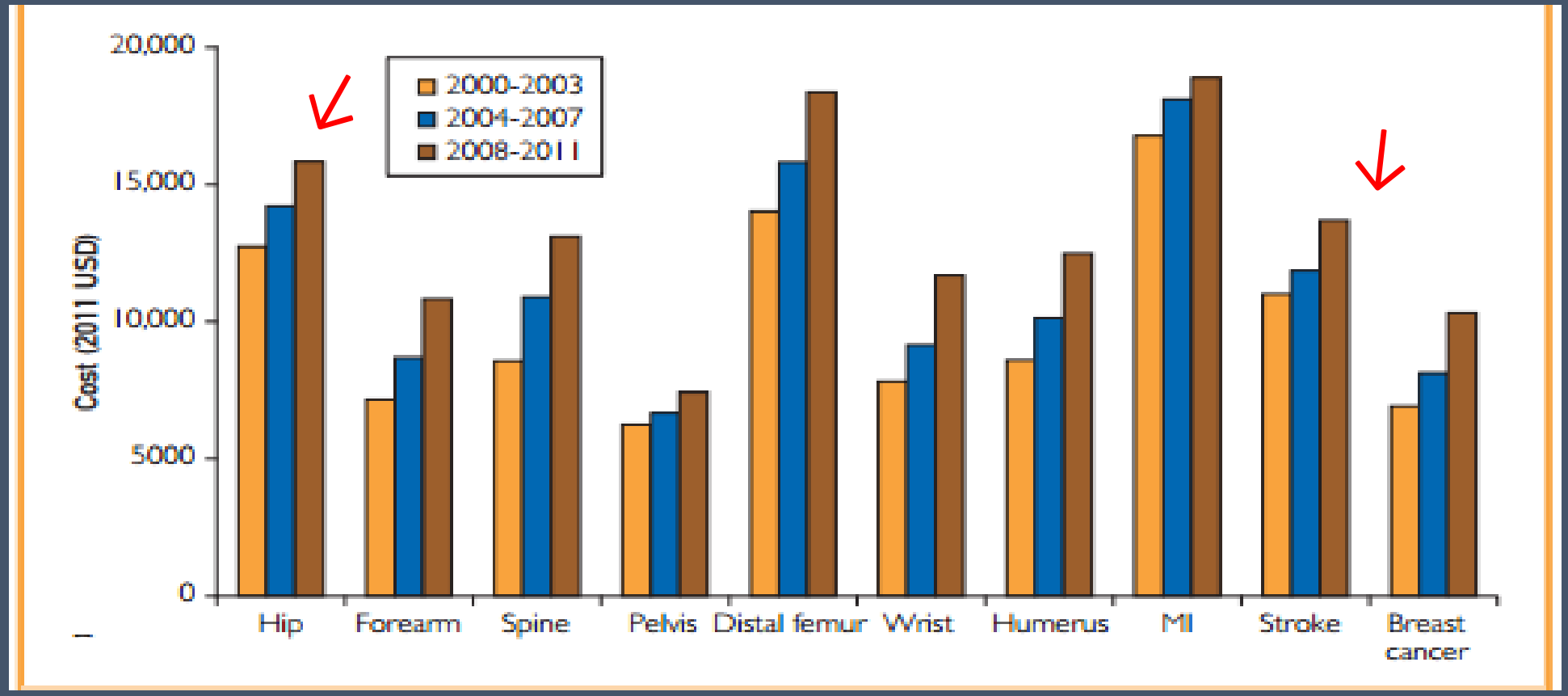


FIGURE 2. (A) Average length of stay and (B) cost[a] per hospitalization for osteoporotic fracture[b] and other diseases of interest. [a]Cost is estimated by applying a cost-to-charge ratio to the reported charges of each admission. All costs are inflated to 2011 dollars using the Consumer Price Index. [b]Only the primary diagnosis was used to determine inclusion; patients with a major trauma diagnosis, and patients receiving revisions or removal of orthopedic devices were excluded.

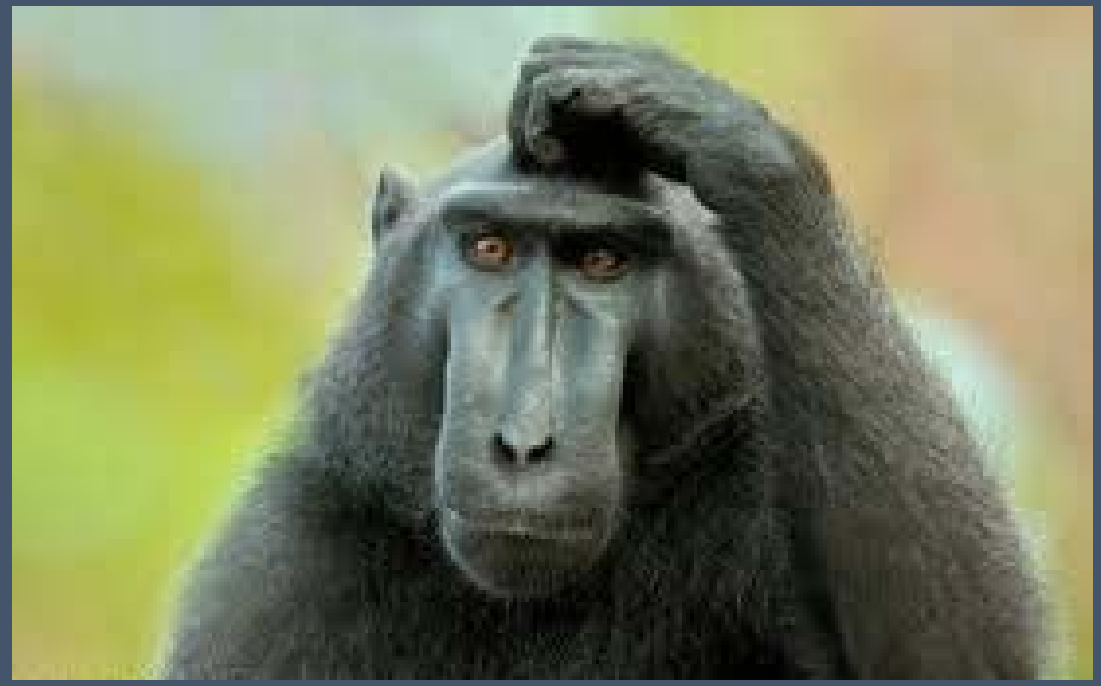
Mayo Clinic Proc 2015

Why are DXA Utilization and Osteoporosis Treatments Decreasing ?

While The annual costs for the care for

osteoporotic fractures are increasing ?

Send Less Confusing Messages



HOW LONG TO TREAT?

- Usually not a question for other chronic diseases
  - Hypertension
  - Dyslipidemia
  - Diabetes
  - CHF

- For Osteoporosis : "Is not, is probably not, perhaps is not, maybe not yet; it'll be over….."

Miller PD Exp Opinion Pharmacotherapy 2003
Bonnick SL JCD 2011
Khosla S et al JCEM 2012
McClung MR et al Am J Med 2012
Strim O et al OI 2015
McClung MR OI 2015
Adler R et al JBMR 2016
Black D and Rosen C NEJM 2016

I Started My Holiday One Year Ago, and I don't know how to judge whether it's over !

Moses and God 1313 BC

Holidays from pharmaceuticals for “our” chronic disease has confused more than clarify

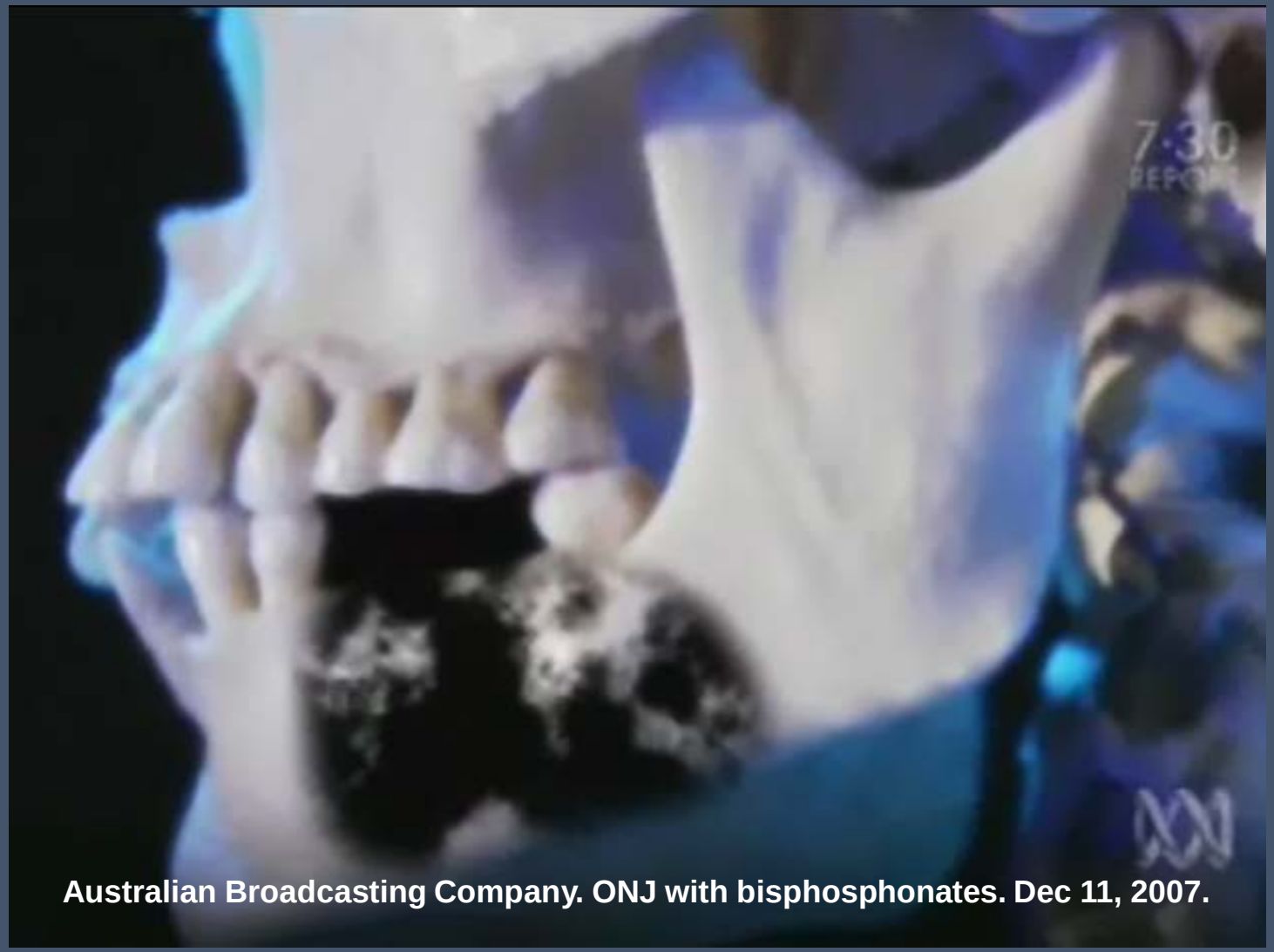
September 9, 2011
FDA Advisory Committee Hearing on Bisphosphonate Duration of Use

1. Little evidence of continual efficacy beyond 5 years

2. Safety concerns re atypical sub trochanteric femur fractures with longer term use

http://www.fda.gov/downloads/dvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM278481.pdf

FEAR



Australian Broadcasting Company. ONJ with bisphosphonates. Dec 11, 2007.

Incident rate: 0.9/100,000 patient year exposure
Baim S and Miller JBMR 2012

ASBMR Reports on Atypical Femoral Fractures

Journal of Bone and Mineral Research

JBMR

Perspective

Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the american society for bone and mineral Research†

Elizabeth Shane‡, David Burr‡, Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, Michael Whyte

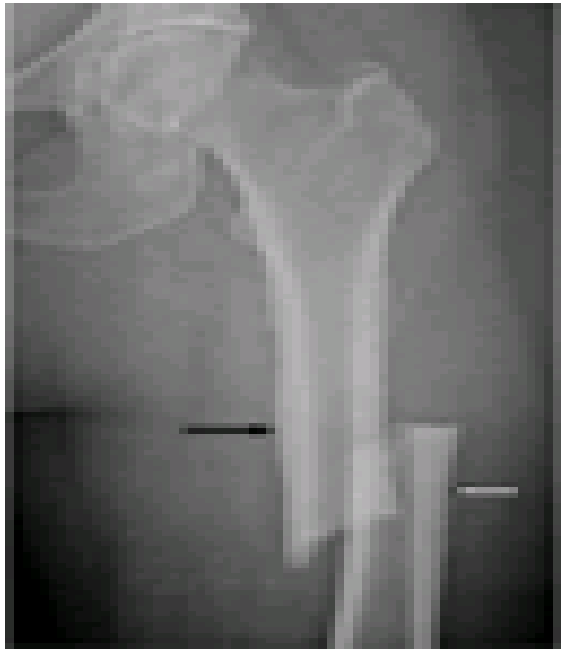
Article first published online: 25 OCT 2010

DOI: 10.1002/jbmr.253

Issue

Journal of Bone and Mineral Research

Volume 25, Issue 11, pages 2267–2294, November 2010



No Causality Established

- Shane E et al JBMR 2010
- Shane E et al JBMR 2014

Different Results With Different Definitions

Criteria	2011 Schilcher	2013 Schilcher
Total # of AFFs	59	80
AFFs w/ BP Use	46 (78%)	49 (61%)
AFFs w/ No BP Use	13 (22%)	31 (39%)
Total # of Subtroch/Shaft	322	277
Subtroch/Shaft w/ BP Use	72 (22%)	69 (25%)
Subtroch/Shaft w/ No BP Use	250 (78%)	208 (75%)

2011 Schilcher NEJM; 2013 Schilcher Bone

Bisphosphonate “Drug Holiday”

- 1. Not a topic of discussion when BP 1st launched (1995)
- 2. Became a consideration after July 9,2002 (WHI JAMA publication) when BP Rx increased in younger post-menopausal women.
- 3. Became more widely discussed after FLEX (Black D et al JAMA 2006), and the better science defining BP Pharmacology became available (Russell G OI, 1970 and Bone 2010).
- 4. FRAX™ also drove the drug holiday discussion in women who, by the FRAX™ calculation had been at low risk before bisphosphonates were started.
- 5. Still, not a standard of care in the USA, though the FDA, and most other “bone” professional societies suggest considering a holiday in lower risk patients after 3-5 years of use.

Miller PD In: Best Practice and Research Clinical Endocrinology and Metabolism 2008; 22 (5): 849-868.

Should Drug Holidays Be Considered? (or Revaluated) ?

- YES

- But consider ONLY in lower risk patients:
- no prior fracture, T-scores > -2.0, and younger age (<65 years)
- and……..
- Because we have no data on patients with steroid use, stage 3-5 CKD, diabetes mellitus and other diseases that alter bone quality and increase fall risk (Parkinsons, MS, etc) one must use caution and clinical judgement in any patient not “fitting” the strict randomization criteria of FLEX (Fosamax Long-Term Extension Black D et al JAMA 2006)

Miller PD JCEM 2016 (in press)

High Risk

- 1. Prior low trauma fracture after 50 years of age
- 2. Low bone mineral density (BMD) and older age (> 65 years)
- 3. High FRAX™ score
- 4. Risk factors not captured in FRAX: falls, diabetes mellitus, higher dose of glucocorticoids, stage 3-5 CKD, frailty.

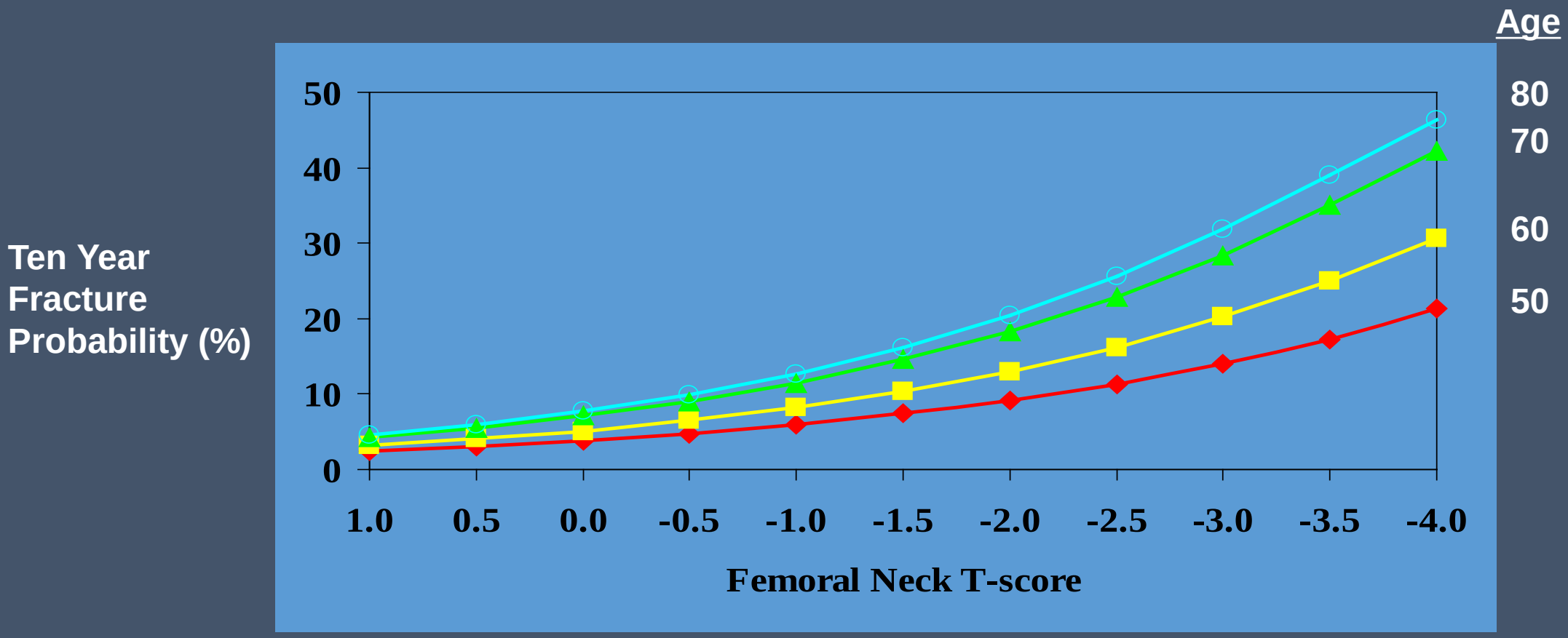
Miller PD Expert Opinion in Pharmacotherapy 2016
Black D and Rosen C NEJM 2016

Prior Fracture Is a Strong Predictor of Future Fractures

Prior Fracture	Future Fractures		
	Wrist	Vertebra	Hip
Wrist	3.3	1.7	1.9
Vertebra	1.4	4.4	2.3
Hip	NA	2.5	2.3

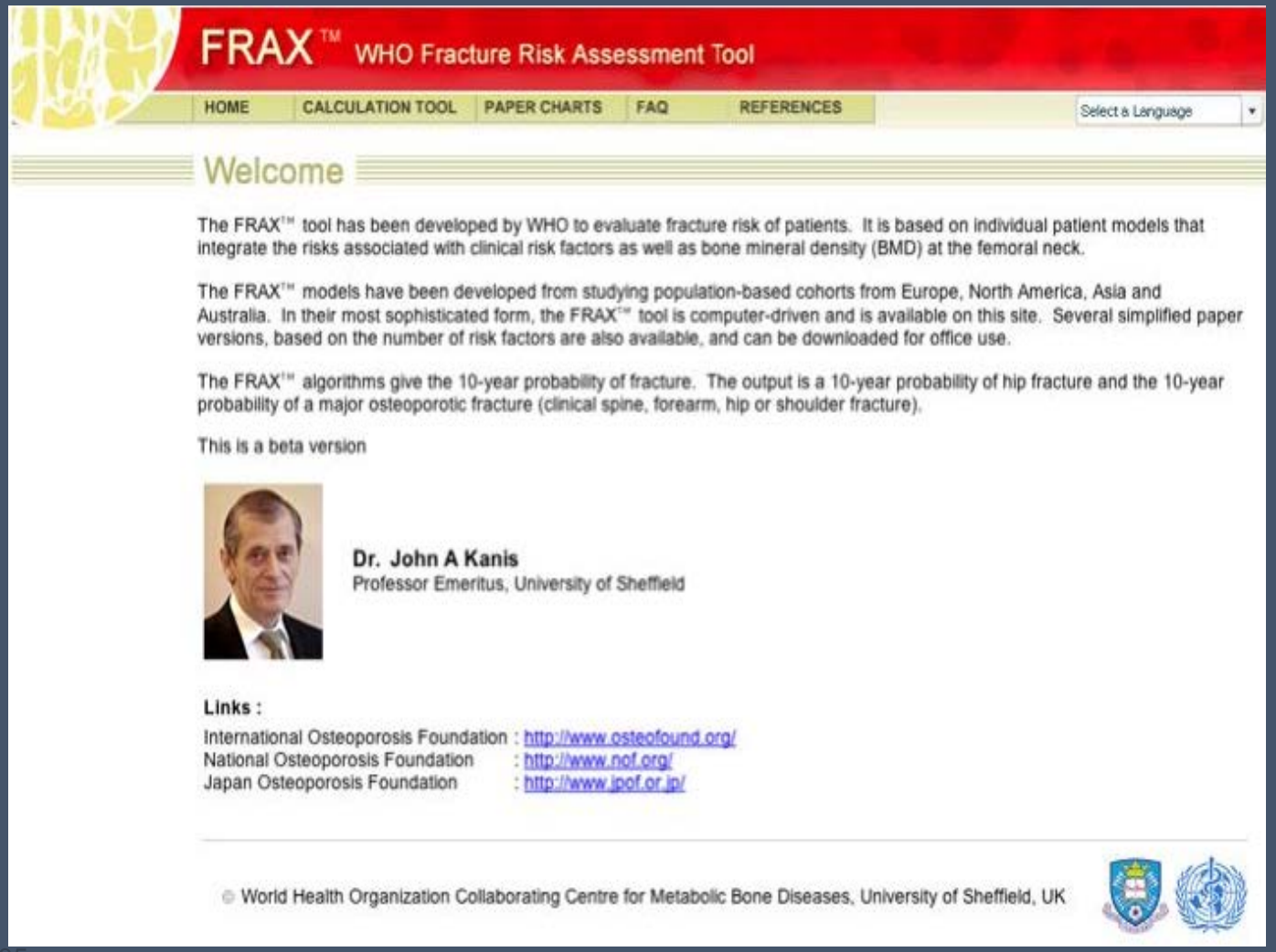
Klotzbuecher CM, et al. *J Bone Miner Res.* 2000;15:721.

Age is an Independent Risk Factor for Osteoporotic Fractures



Adapted from: Kanis JA et a. *Osteoporosis Int*. 2001;12:989-995.

FRAX™: The WHO Fracture Risk Assessment Tool www.shef.ac.uk/FRAX/



WHO Risk Factors Estimate 10-year Risk of Fracture

→Age (40-90)

- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Ever long-term use of glucocorticoids
- Rheumatoid arthritis or
- Other secondary causes
- Alcohol intake 3 or more units daily
- Low BMD

Treat:

10 year risk major fracture > 20%

Hip fracture > 3%

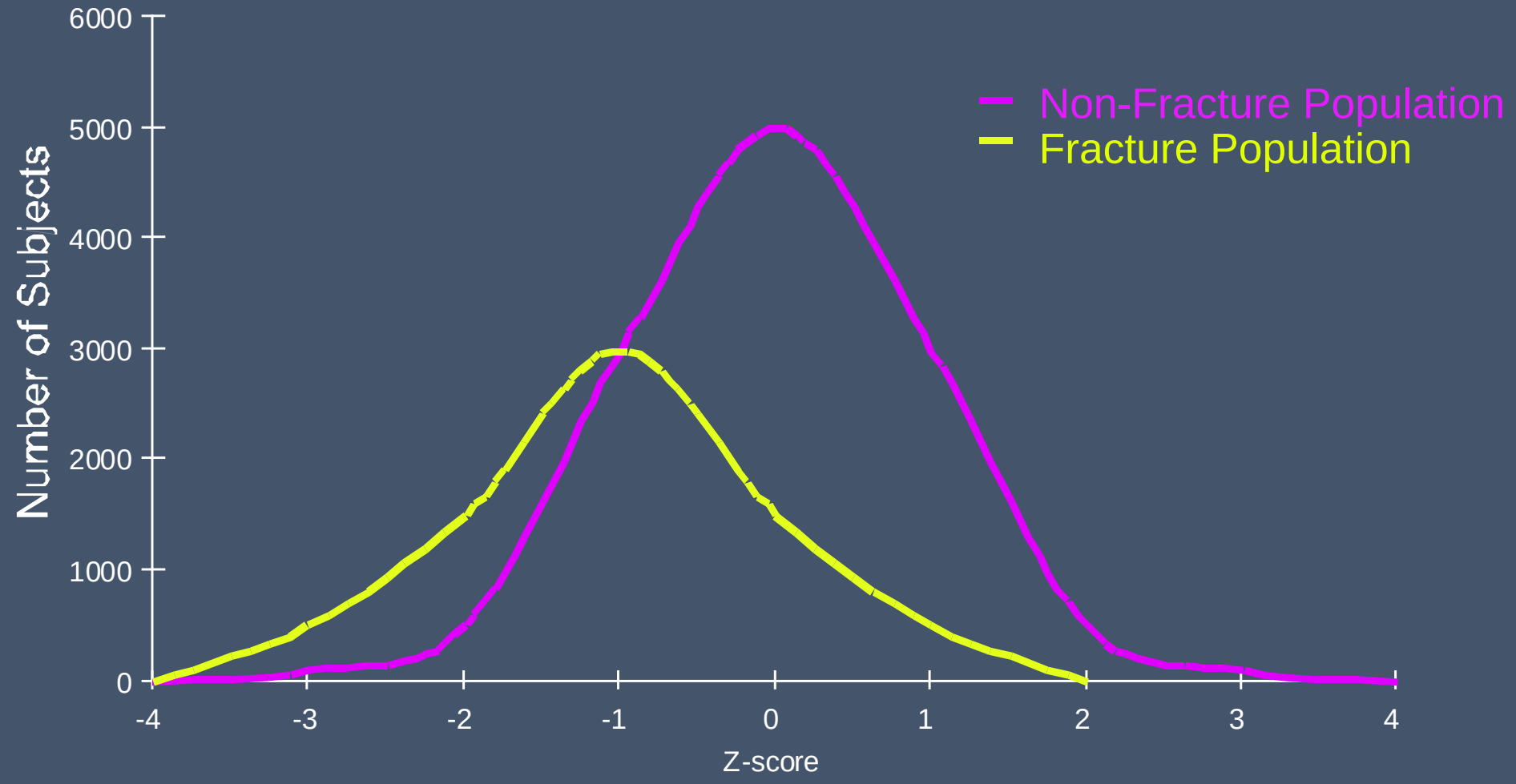
Thresholds heath-economic modelling

Kanis, et. al., Osteoporosis Int, 2008; 19:385-397

Fracture Risk Is a Gradient, Not a Threshold

- Fracture risk is similar at comparable age for a:
  - T-score = −2.4 (osteopenia) and T-score = −2.6 (osteoporosis) in spite of different diagnostic categories
- Fracture risk is much higher at comparable age for a:
  - T-score of −5.0 compared with a T-score of −2.5 in spite of the same diagnostic categories (osteoporosis)

BMD Overlaps in Patients With and Without Fractures



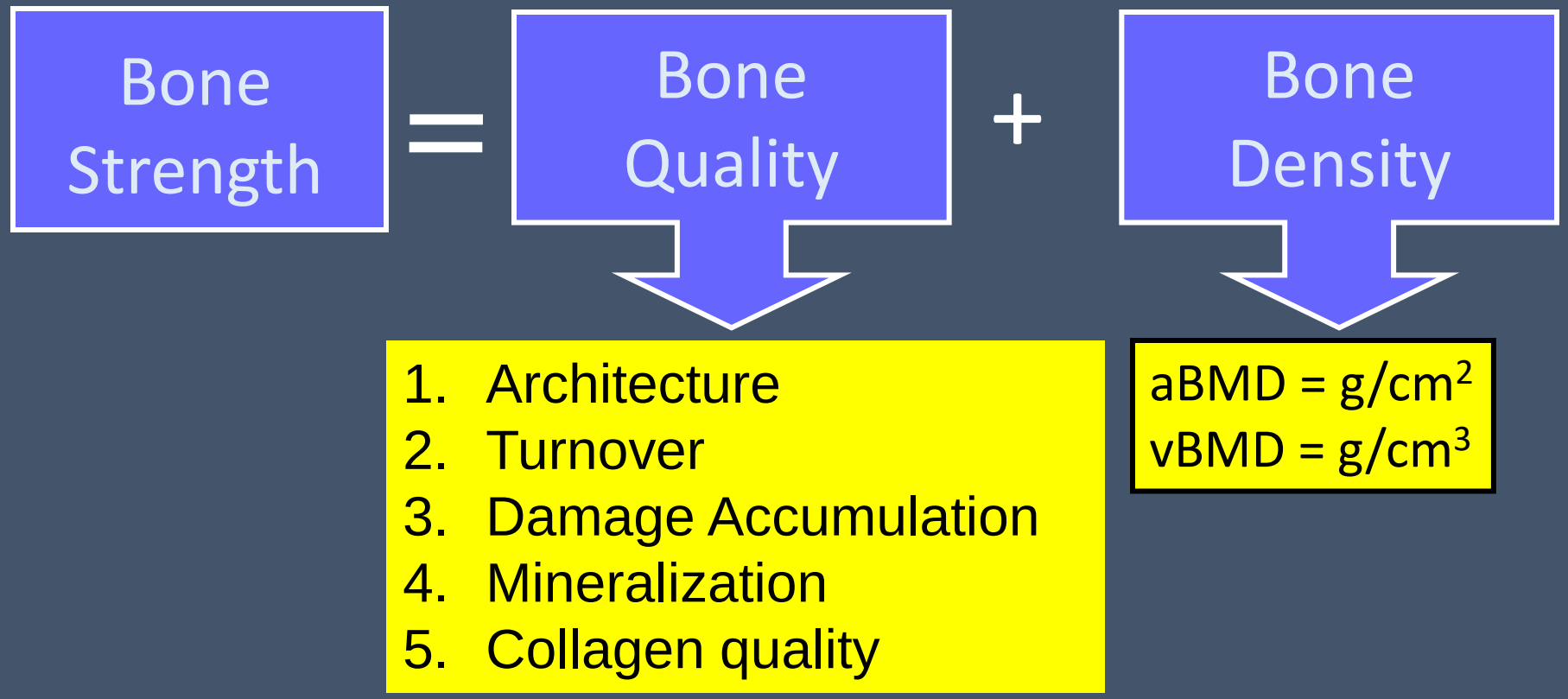
Watts NB et al Endocrine Practice 2010

Bone Strength

- Bone Density
- Bone Quality

Osteoporosis

Compromises Bone Strength
Increases Risk of Fracture



Adapted from NIH Consensus Development Panel on Osteoporosis. JAMA 2001

How Do We Measure Bone Quality?

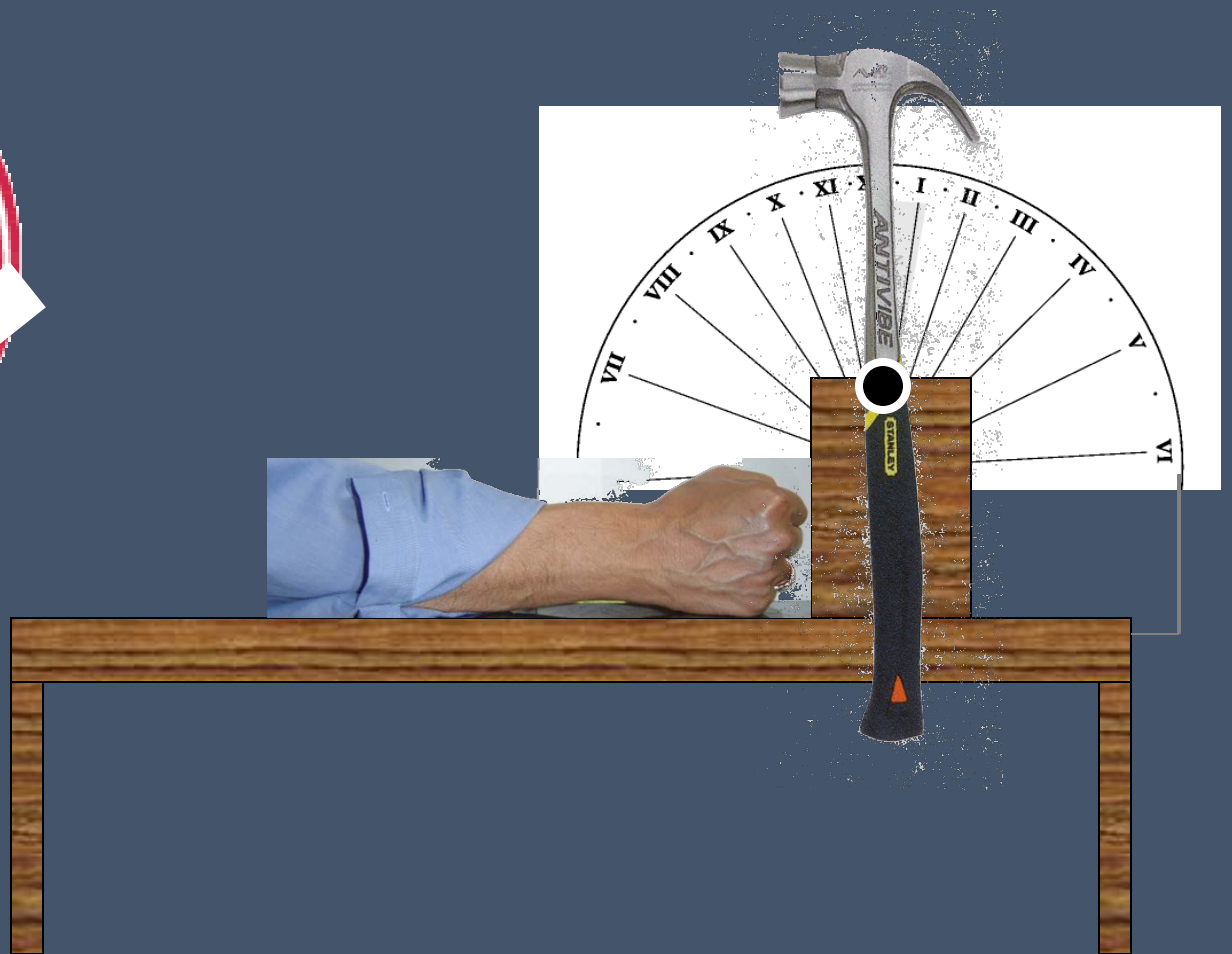
- There is no readily available clinical method for assessing bone quality or microarchitecture
- BMD and bone turnover markers will continue to play a role in the assessment of response to osteoporosis therapy
- Bone quality is dependent on factors other than BMD such as: bone turnover, secondary mineralization, cortical porosity, bone size, health of osteocytes, and the health and structure of trabeculae

TBS (trabecular bone score) a new “Grey Scale” derived from DXA is a partial measure of bone quality

Seeman E JBMR 2008

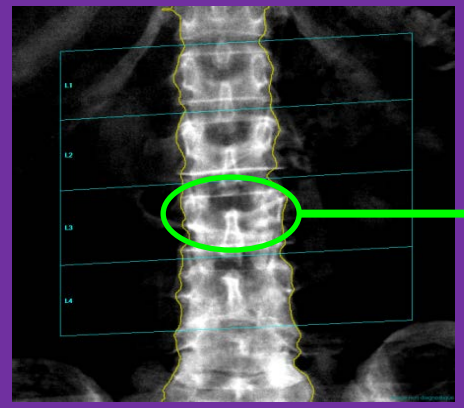
The Office-Based Bone Quality Measurement Tool

Dr. P. Miller's Patented Bone Quality Meter

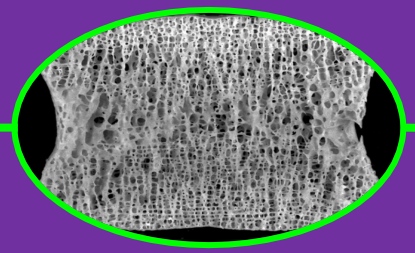


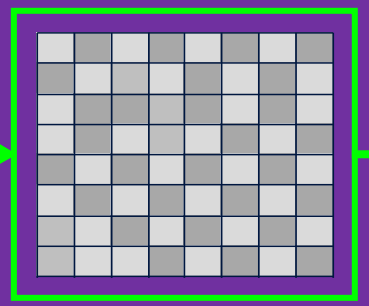
Example of Different Bone Texture (TBS) Despite Same L1-L4 BMD

Two patients with Same L1-L4 BMD



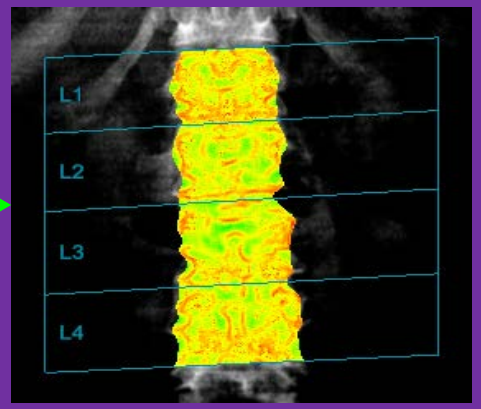
Normal trabecular Bone architecture

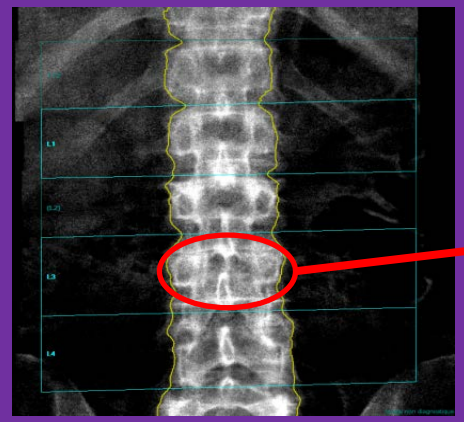




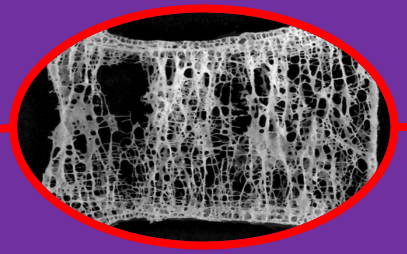
Homogeneous: High TBS

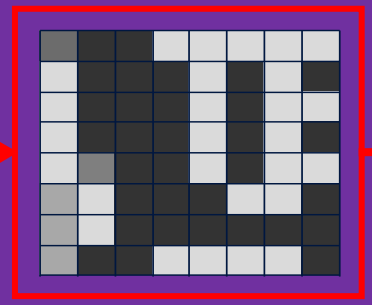
TBS L1-L4: 1.457





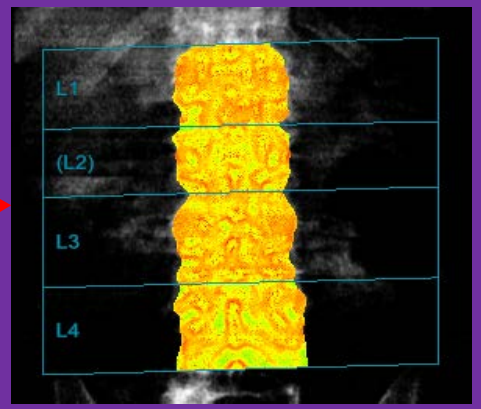
Degraded trabecular bone architecture





Heterogeneous: Low TBS

TBS L1-L4: 1.132



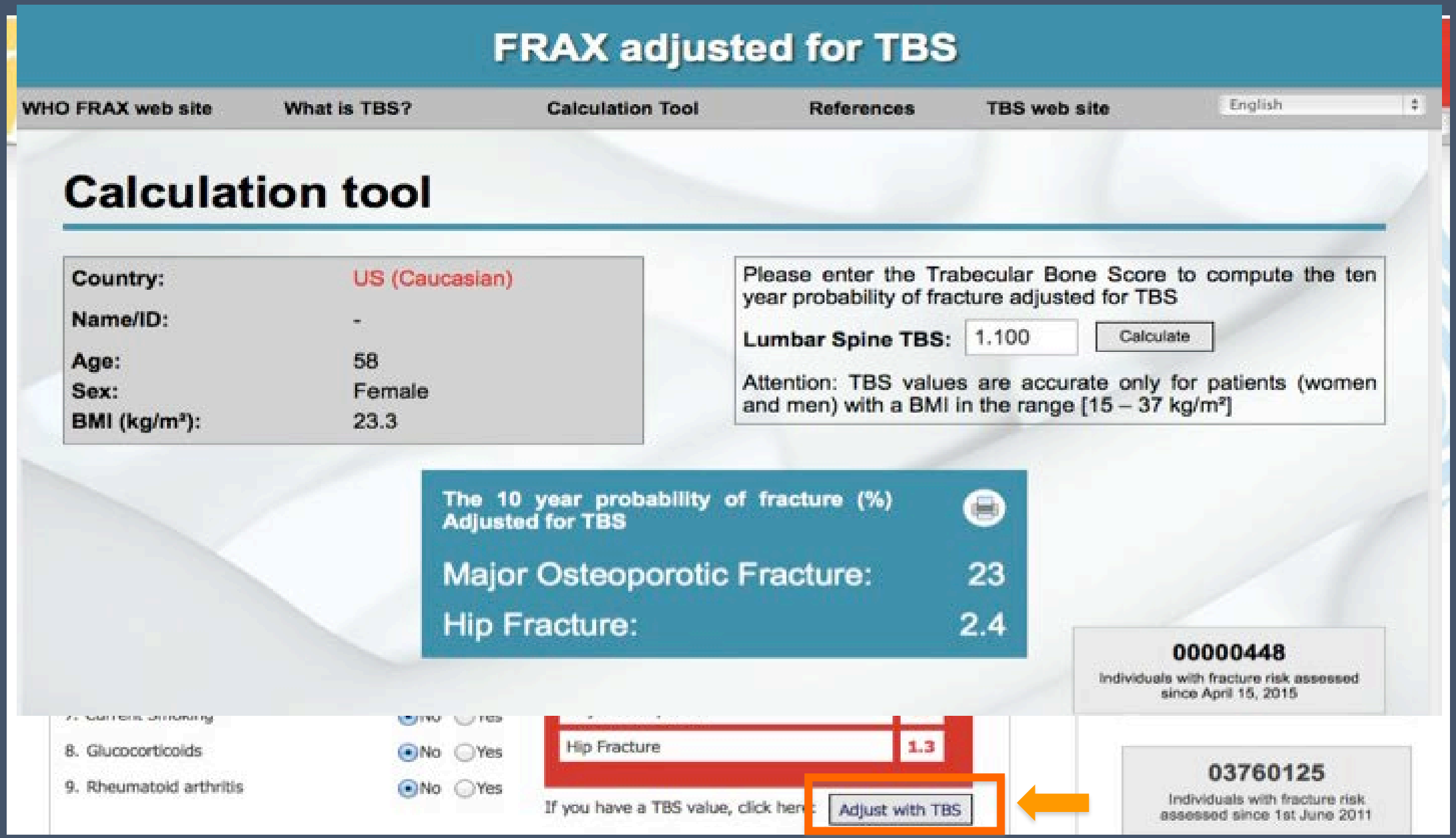
Adapted from Silva et al. J Bone Miner Res. 2014, 29:518–530

TBS: How is the Number Interpreted?

BMD	TBS
Normal T-score ≥ -1	normal TBS ≥ 1.350
Osteopenia -1 < T-score < -2.5	partially degraded 1.200 < TBS < 1.350
Osteoporosis T-score ≤ -2.5	degraded TBS ≤ 1.200

Silva et al. J Bone Miner Res. 2014, 29:518–53
http://www.medimaps.fr/tbs-insight

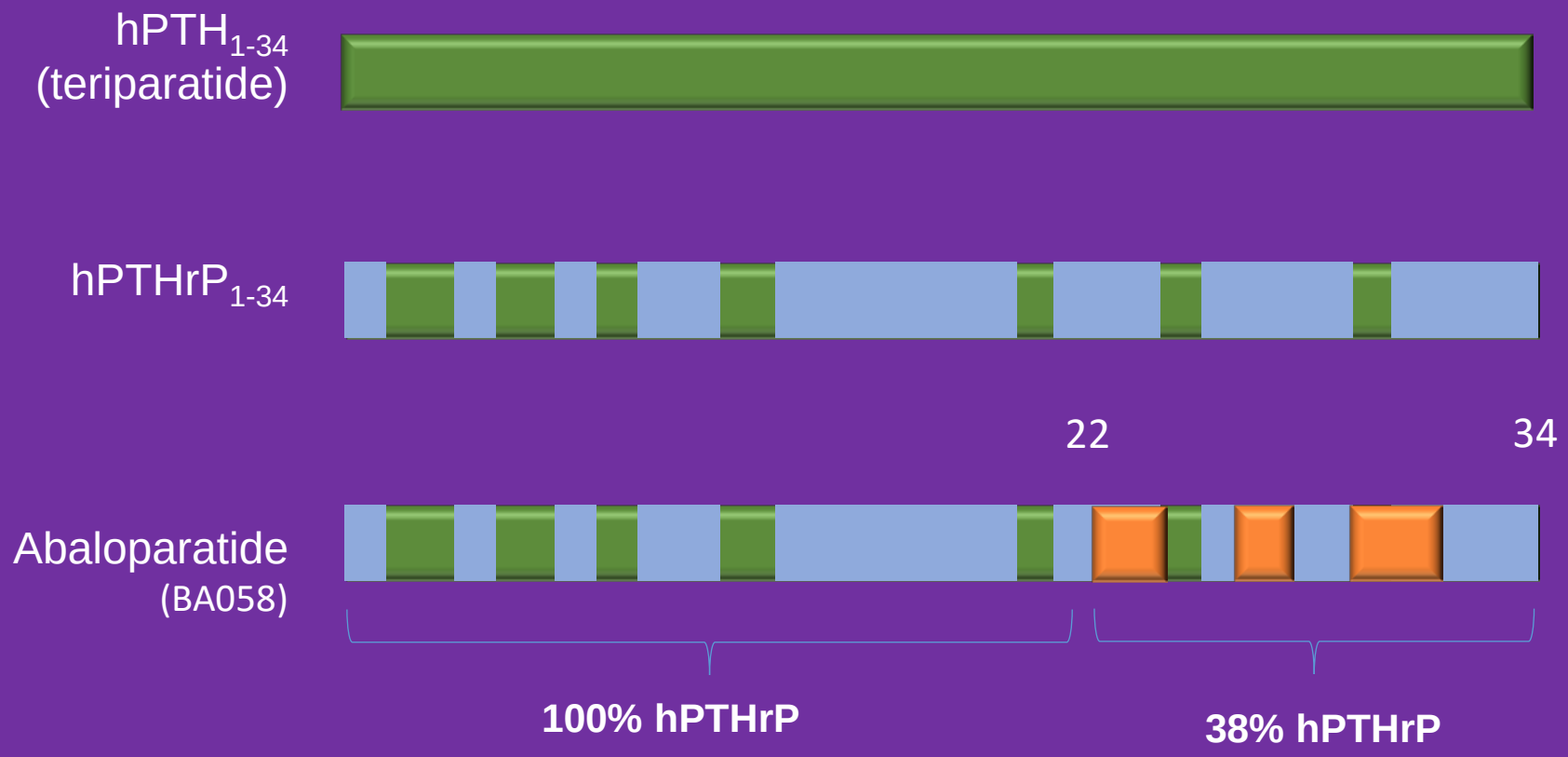
TBS Data Can be Used to Adjust FRAX



Efficacy Data Based upon Pivotal Clinical Trials

Agent	Vertebral	Nonvert	Hip
Estrogen	+	+	+
Alendronate	+	+	+
Risedronate	+	+	+
Zoledronic acid	+	+	+
Ibandronate	+	- *	-
Denosumab	+	+	+
Strontium	+	+	-*
Raloxifene	+	-	-
Calcitonin	+	-	-
Teriparatide	+	+	-

Novel Amino-Acid Sequence of Abaloparatide and PTH/PTHrP homology

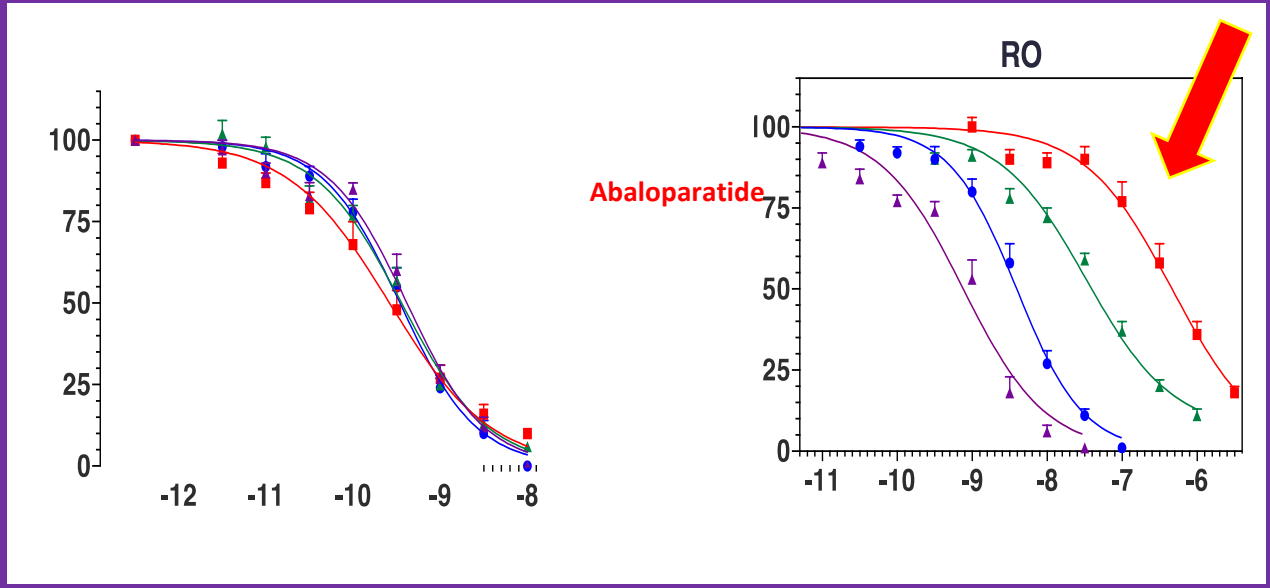


Functionally important amino acid replacements

at positions between residues 22-34

Abaloparatide

- Abaloparatide is a novel synthetic peptide analog of hPTHrP(1-34)
- Enhanced PTH1 Receptor RG/RO selectivity as compared to PTH or PTHrP (ENDO 2014 Hattersley et al)



Preferential stimulation of RO PTH osteoblast receptor my induce less OB production of Rank-L

- Preclinical demonstration of significant BMD increases, restoration of bone microarchitecture, and increased bone strength (ENDO 2015 Bahar et al)

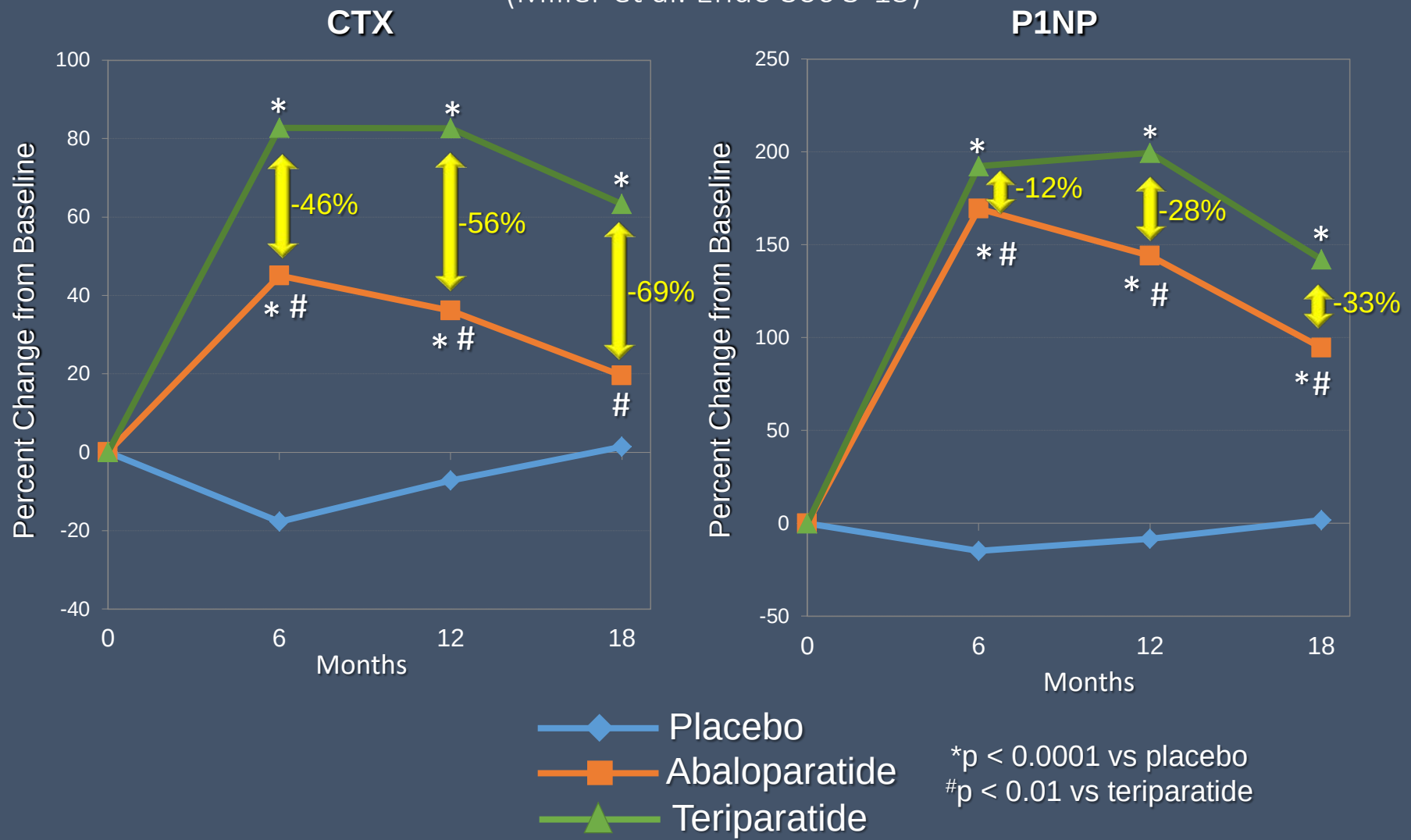
Phase 3 Trial Design of Abaloparatide Clinical Trial

N = 2463

Miller PD et al, Endocrine Society 2015

Changes in Bone Turnover Markers: Abaloparatide vs. Teriparatide vs. Placebo

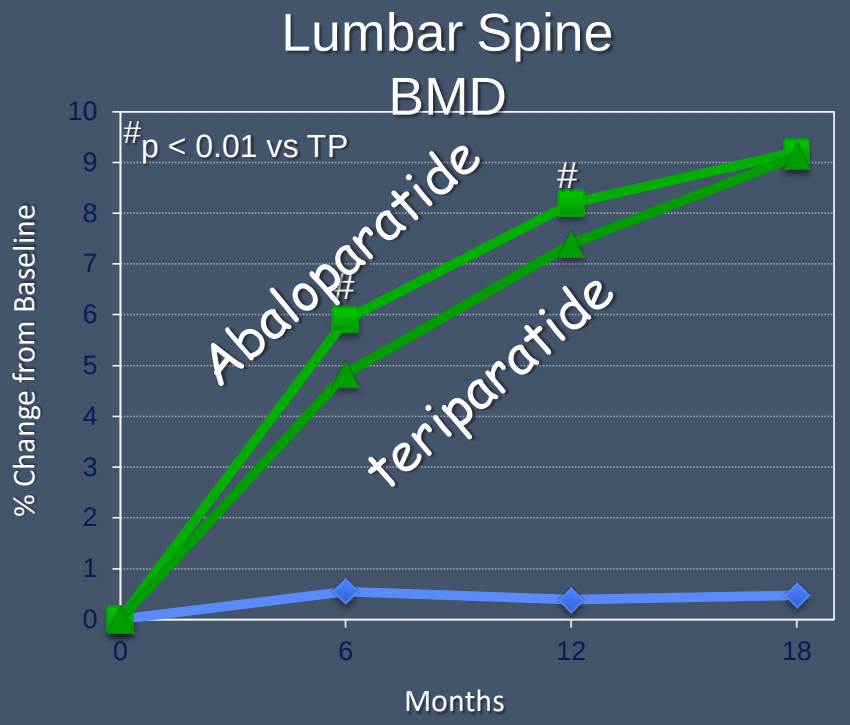
(Miller et al. Endo Soc 3-15)

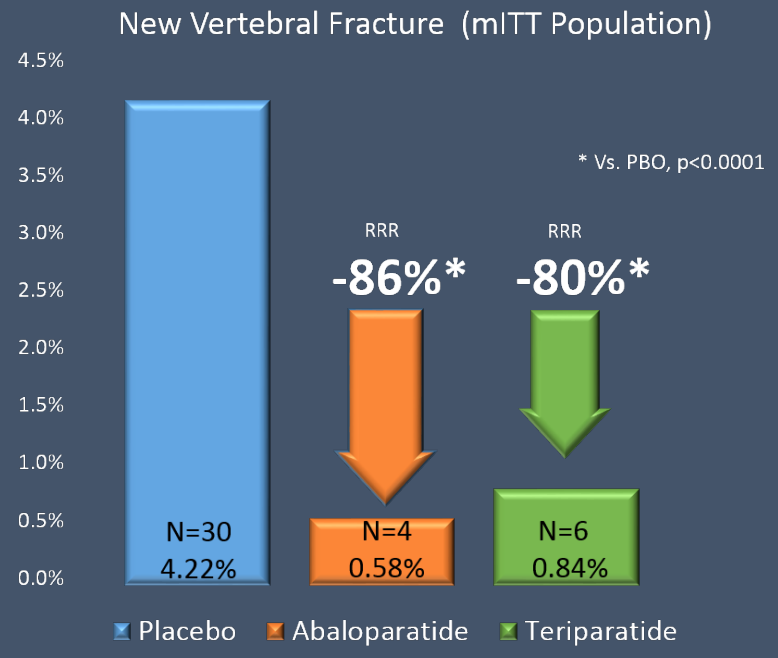


*p < 0.0001 vs placebo

#p < 0.01 vs teriparatide

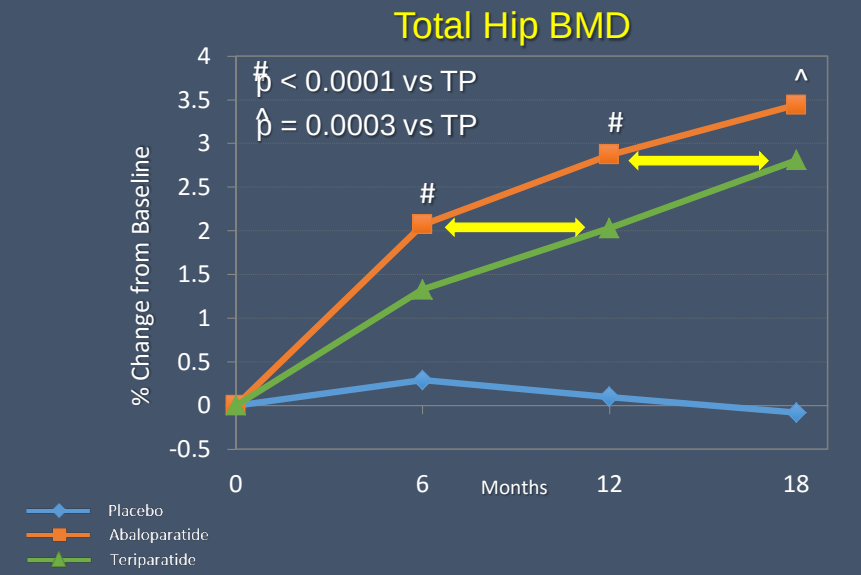
Changes in BMD at the Spine and Reduction in New Vertebral Fractures: All 3 Groups

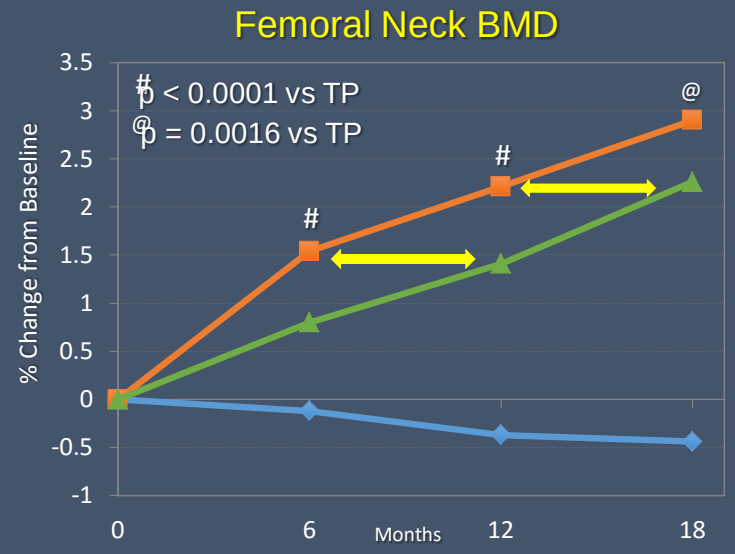


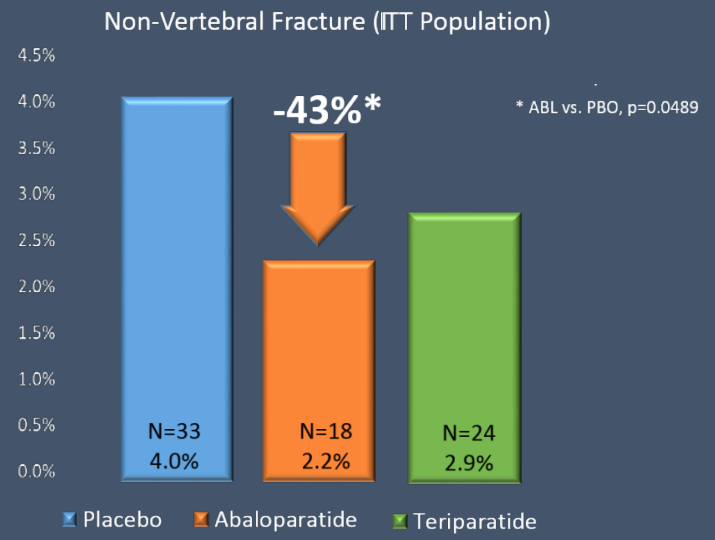


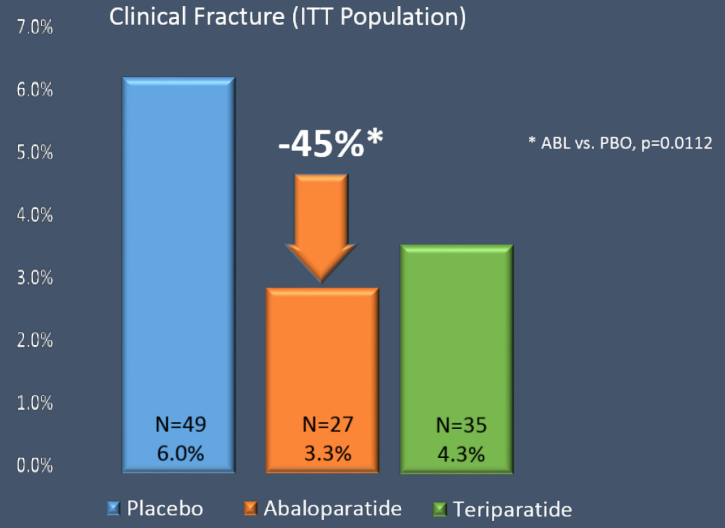
(Miller et al. Endo Society, 3-15)

Changes in BMD at Non-Vertebral Sites and NVF Risk Reduction: All 3 Groups



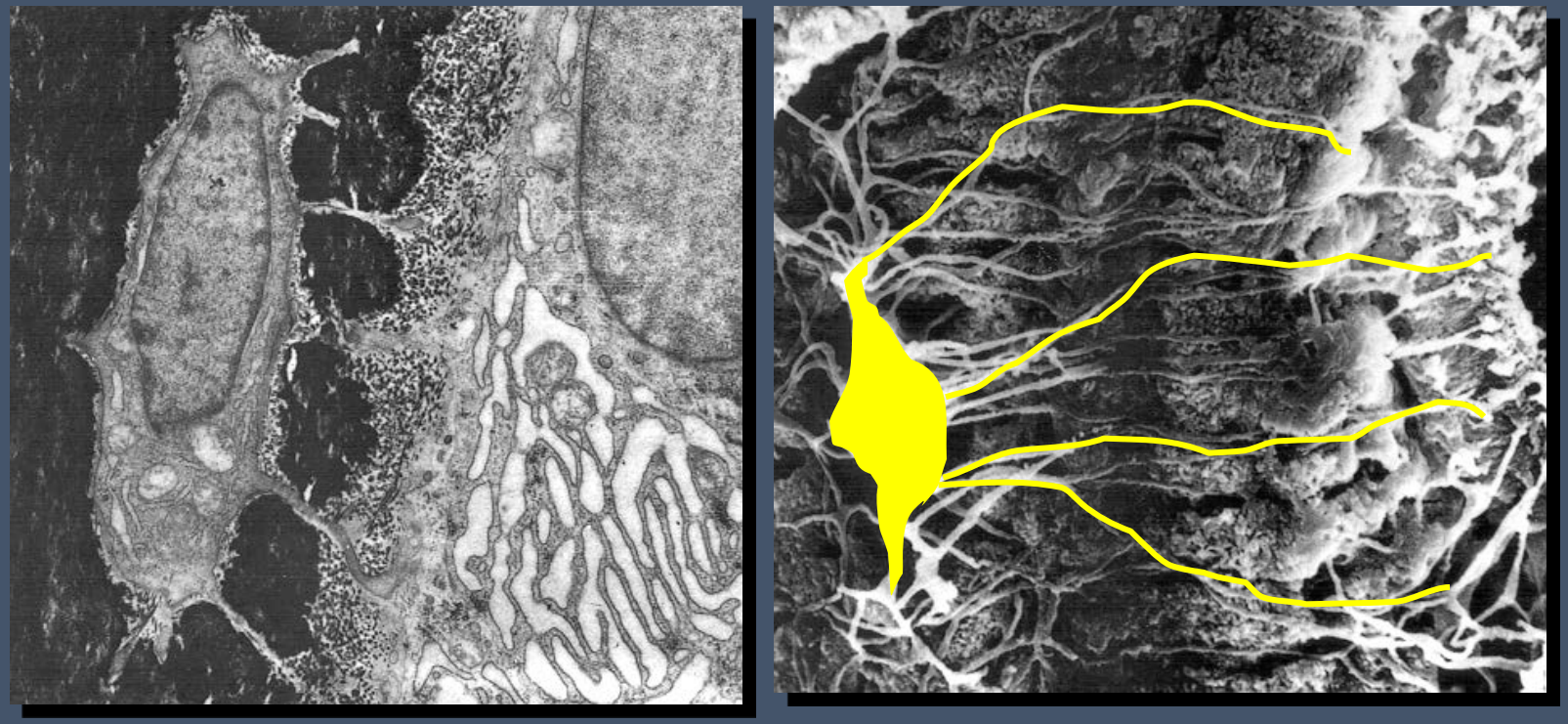






Miller PD et al Endocrine Society 2015

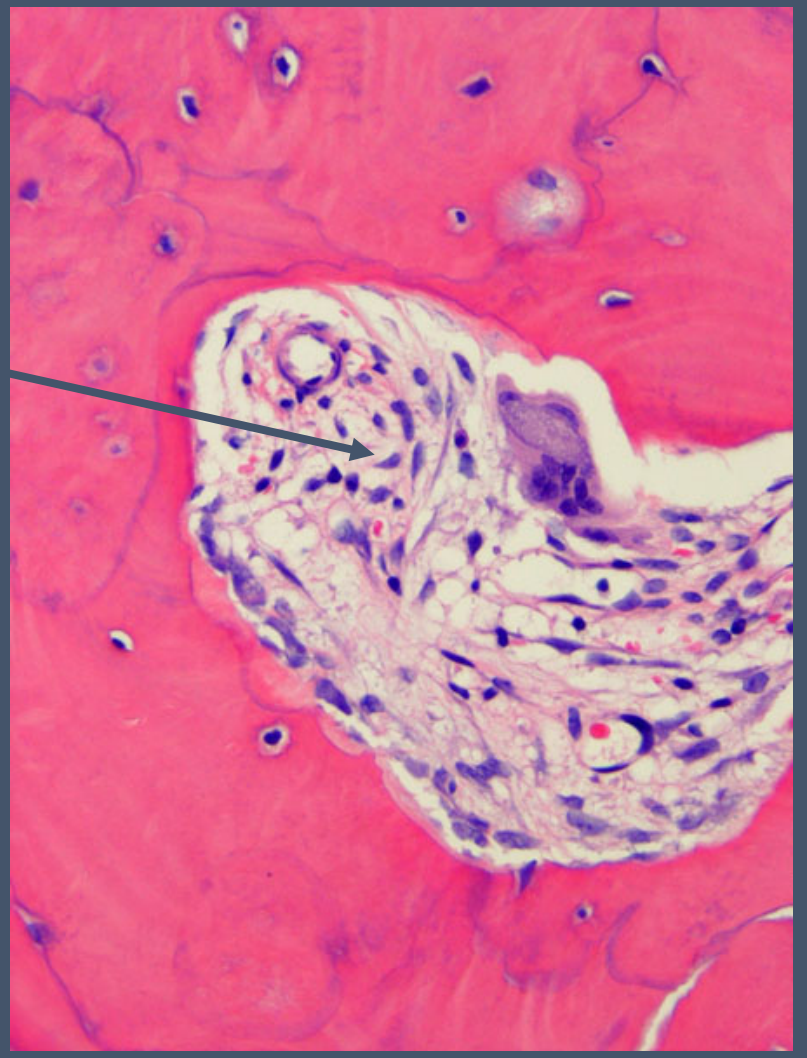
Osteocyte – the mechanosensor



Marotti G, 1996

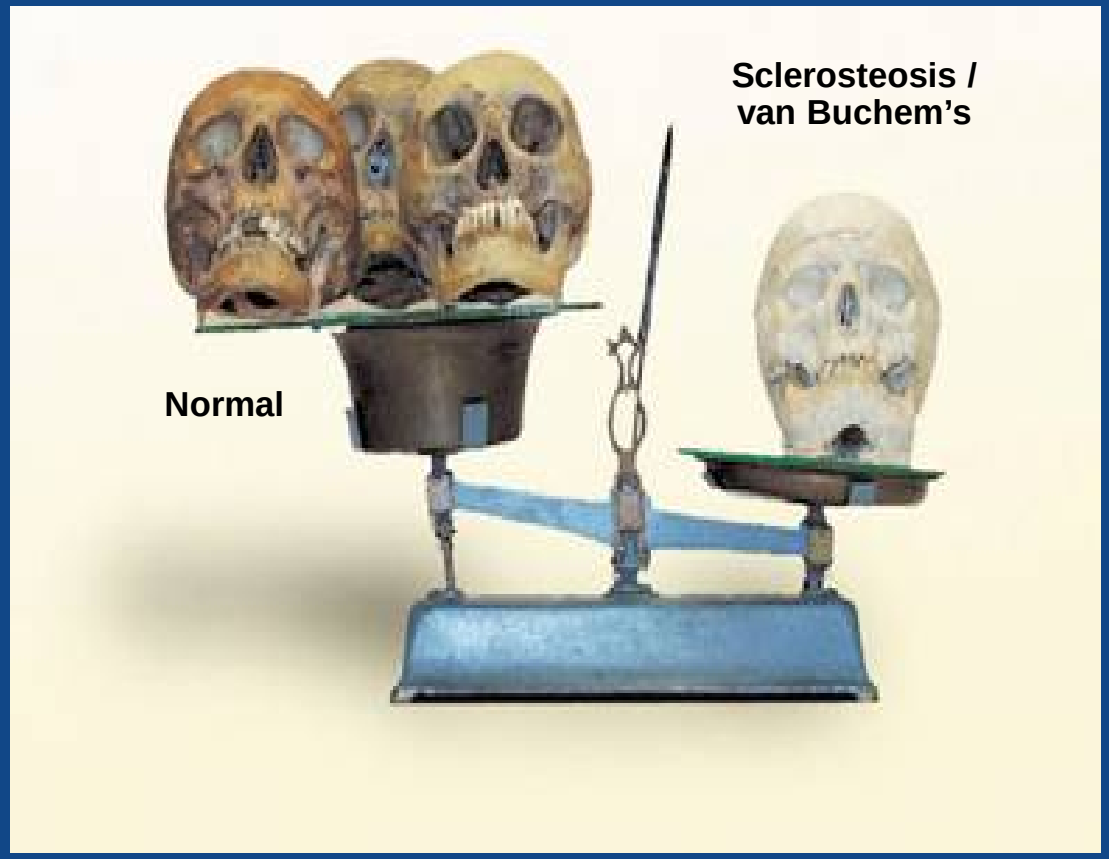
Osteocytes

- Secrete sclerostin to limit bone marrow stromal cell differentiation into osteoblasts and inhibit bone formation



Bonewald LF and Johnson ML. *Bone.* 2008;42:606.

Sclerosteosis



Increased bone mass throughout skeleton.

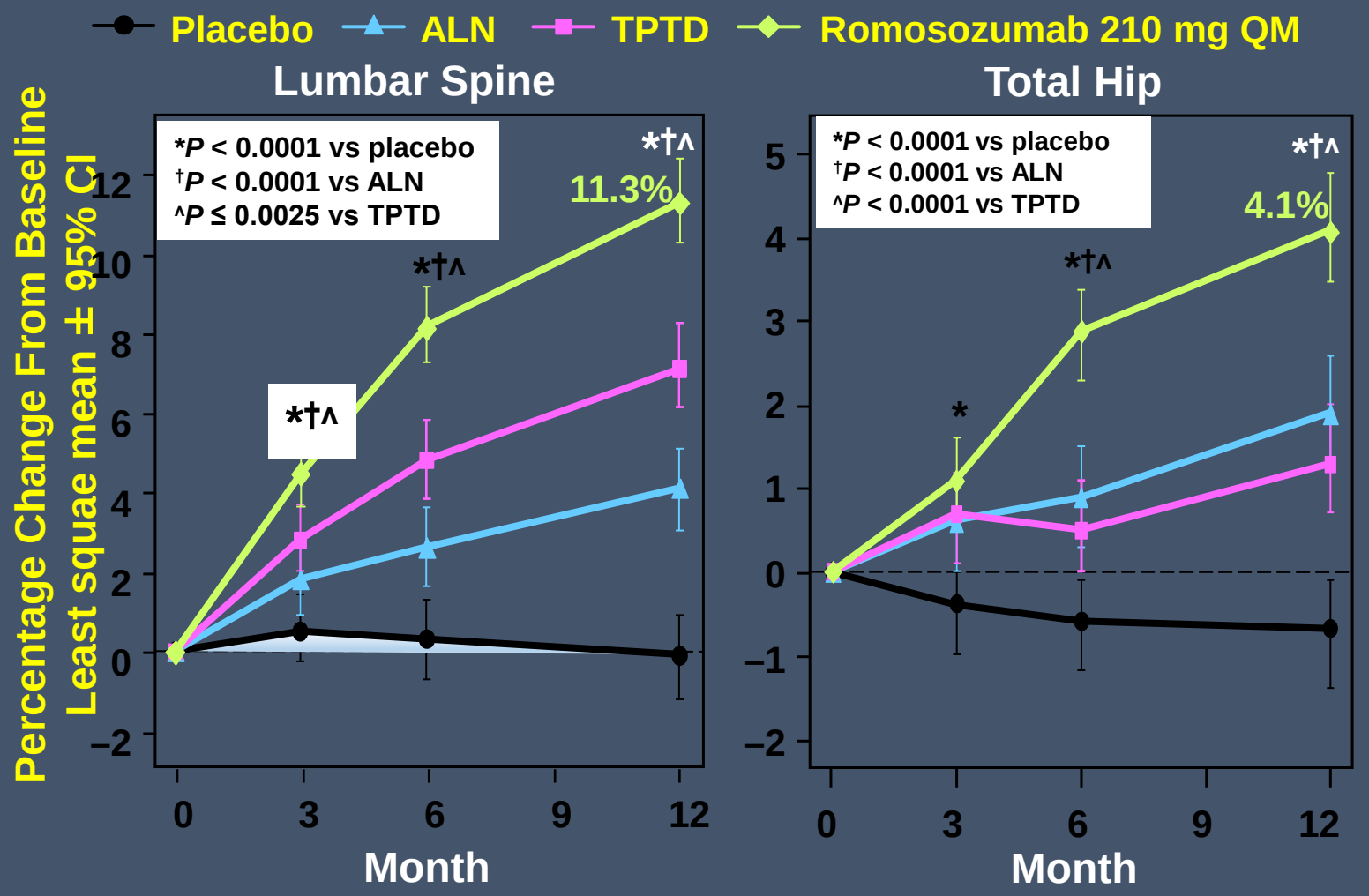
Very low fracture risk

due to *absence* of sclerostin (SOST) - a bone formation inhibitor

Photo: Janssens and Van Hul.
Hum Mol Genet. 2002;11:2385-93.

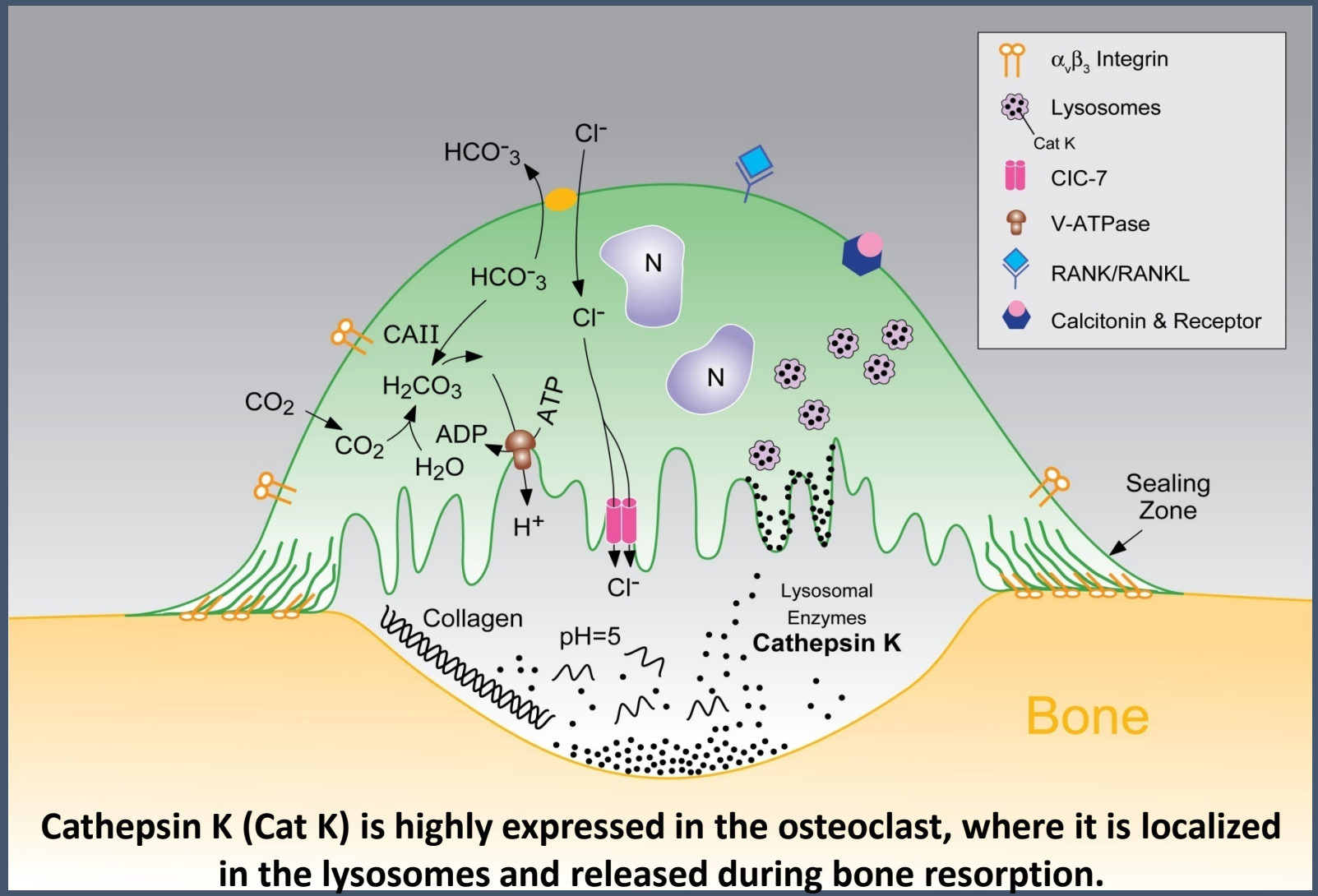
Anti-Sclerostin Antibody (Romosozumab)

BMD – Phase2- effects on BMD*



McClung MR et al. NEJM, 2014.

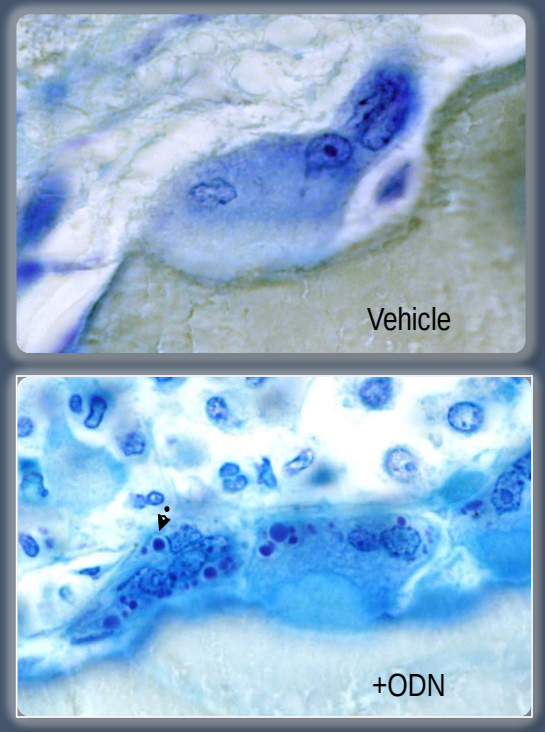
Bone **Resorption by** Osteoclasts

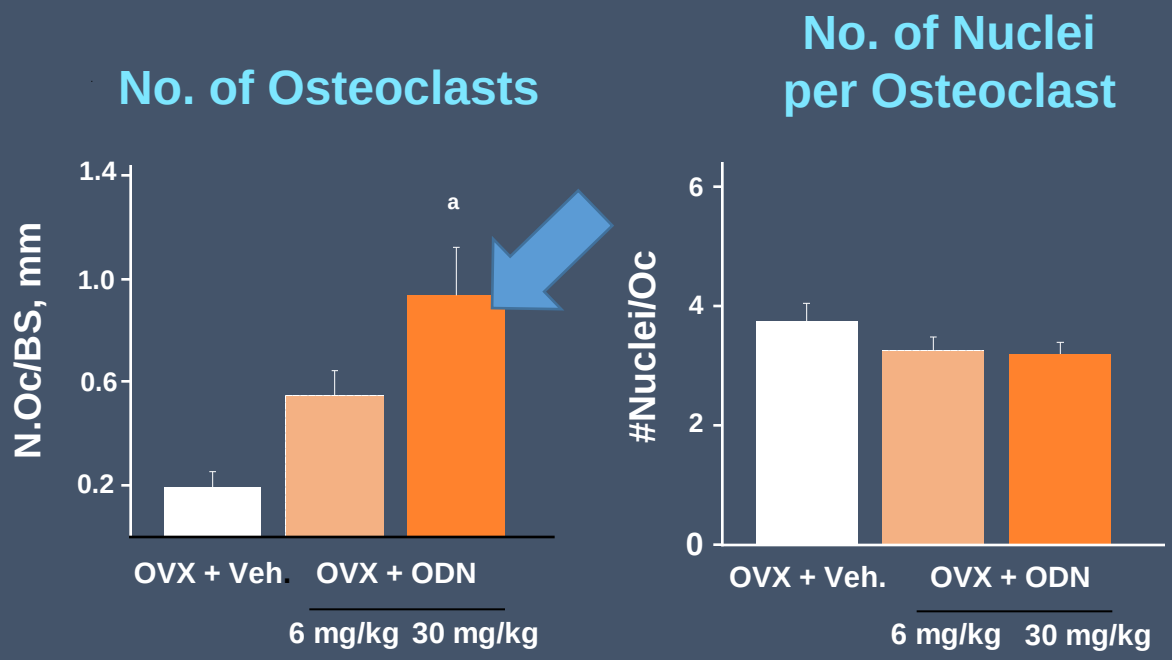


Cathepsin K (Cat K) is highly expressed in the osteoclast, where it is localized in the lysosomes and released during bone resorption.

Rodan SB et al. *IBMS BoneKey.* 2008;5:16–24.

Odanacatib Treatment Increases Osteoclast Number in OVX Monkeys





- "Frustrated" osteoclasts with cytoplasmic granules containing degraded collagen fragments, TRAP, and other lysosomal enzymes

[a]$P<0.05$ vs. Veh.

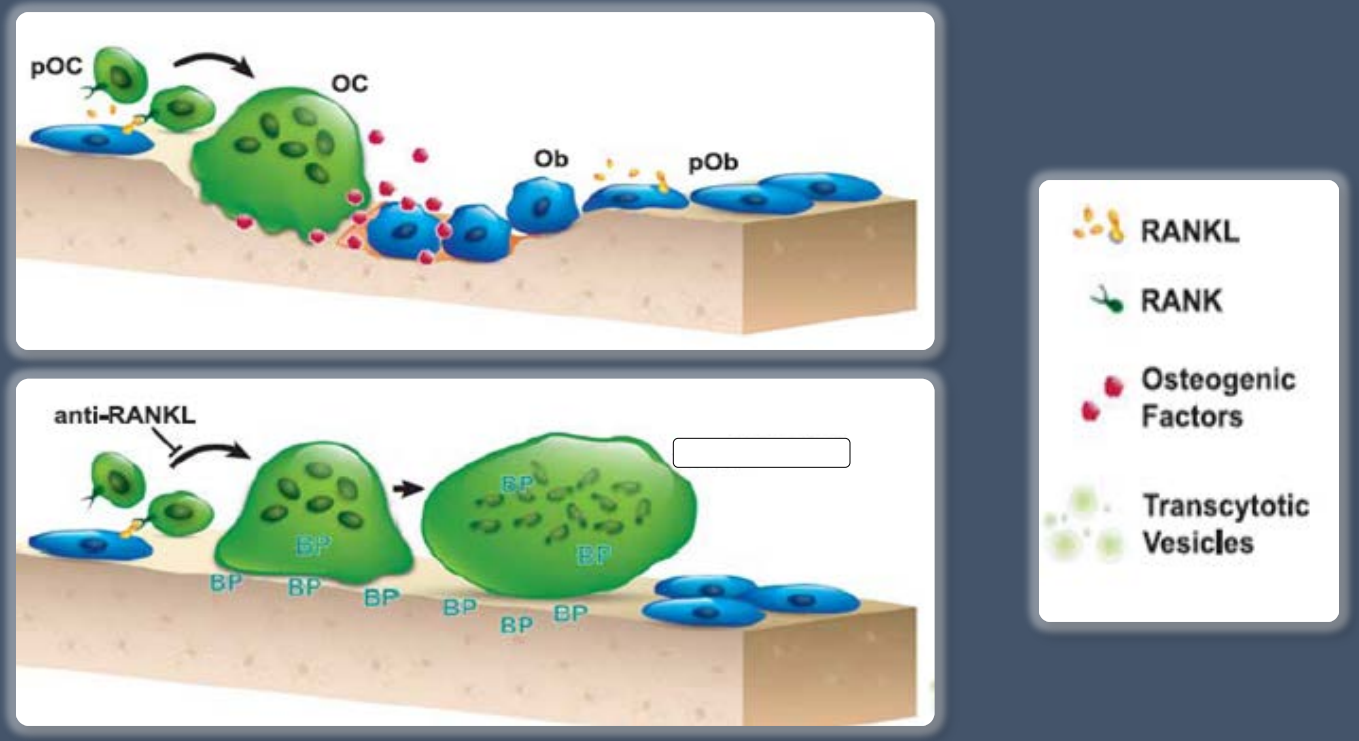
Masarachia PJ et al. *J Bone Miner Res*. 2012;27:509–523.

Traditional Antiresorptives Reduce Bone Formation While Inhibiting Bone Resorption

- BPs: change OC morphology and decrease their activity
- Denosumab: reduces the number of OCs
- Both compounds: fewer resorption pits, reduced new bone formation

Vehicle

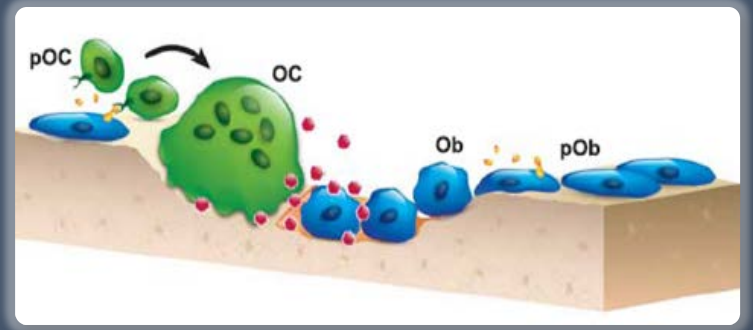
BP or denosumab

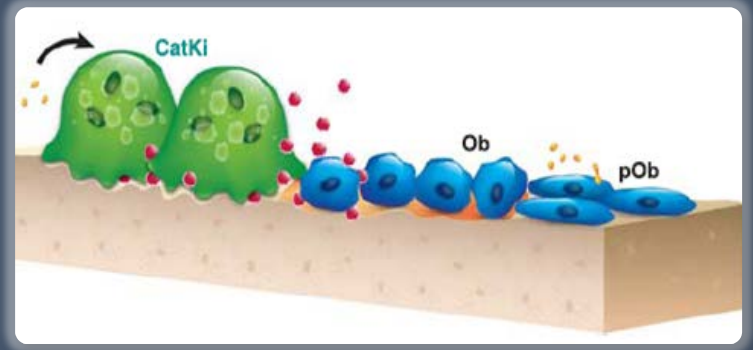


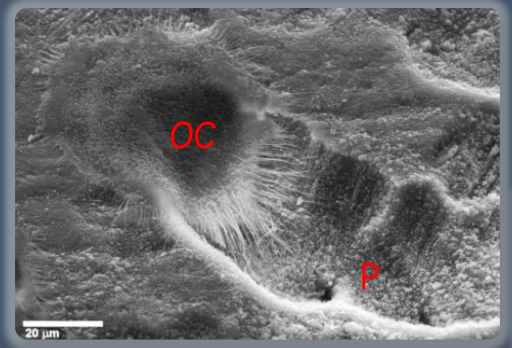
Duong LT. *BoneKEy Reports*.2012;1. Article no. 67.
Leung P et al, *Bone*. (2011) 49:623–635.

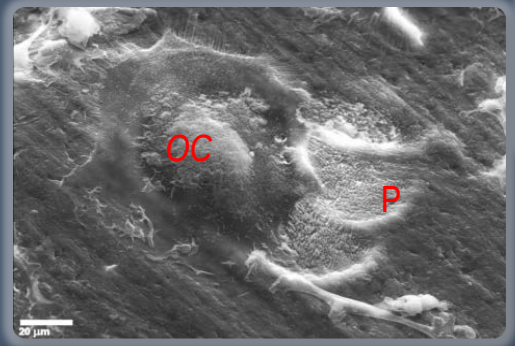
Odanacatib Inhibits Bone Resorption While Preserving Bone Formation

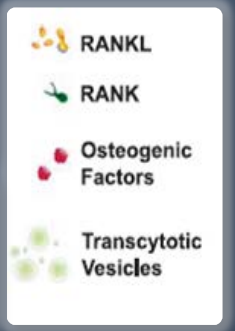
- Odanacatib reduces the activity of Cat K in and outside the OC
  - Same number of resorption pits, but shallower
  - Does not alter signals back to the OB
  - Allows new bone formation to continue







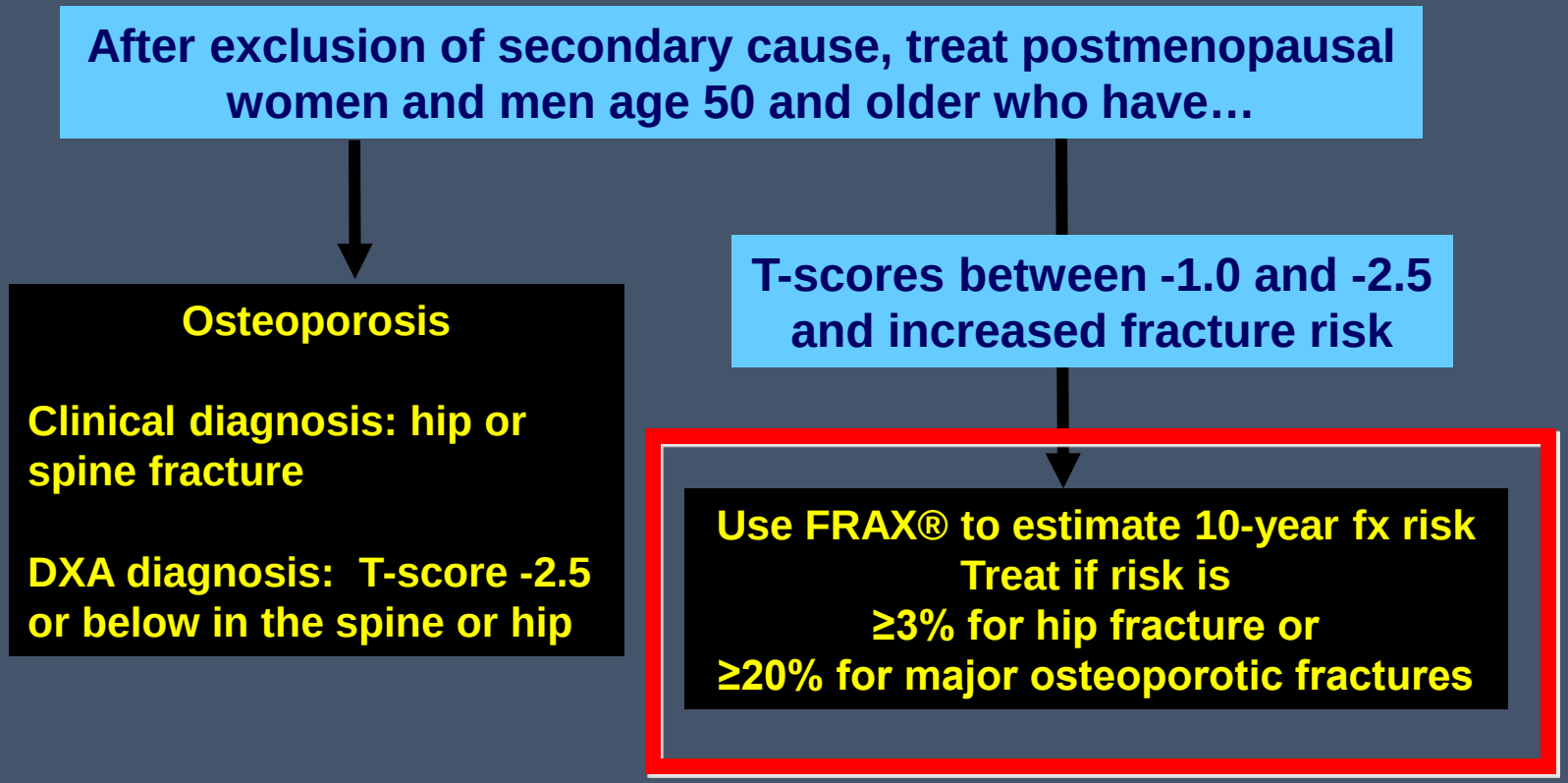




Cat K = cathepsin K; pOC = pre-osteoclast; OC = osteoclast; Cat Ki = Cat K inhibitor; Ob = osteoblast; pOb = pre-osteoblast; P = resorption pit; RANK = receptor activator of nuclear factor kappa-B; RANKL = RANK ligand .

Duong LT. *BoneKEy Reports*.2012;1. Article no. 67.
Leung P et al. *Bone*. 2011;49:623–635.

WHOM TO TREAT
NOF GUIDELINES 2008

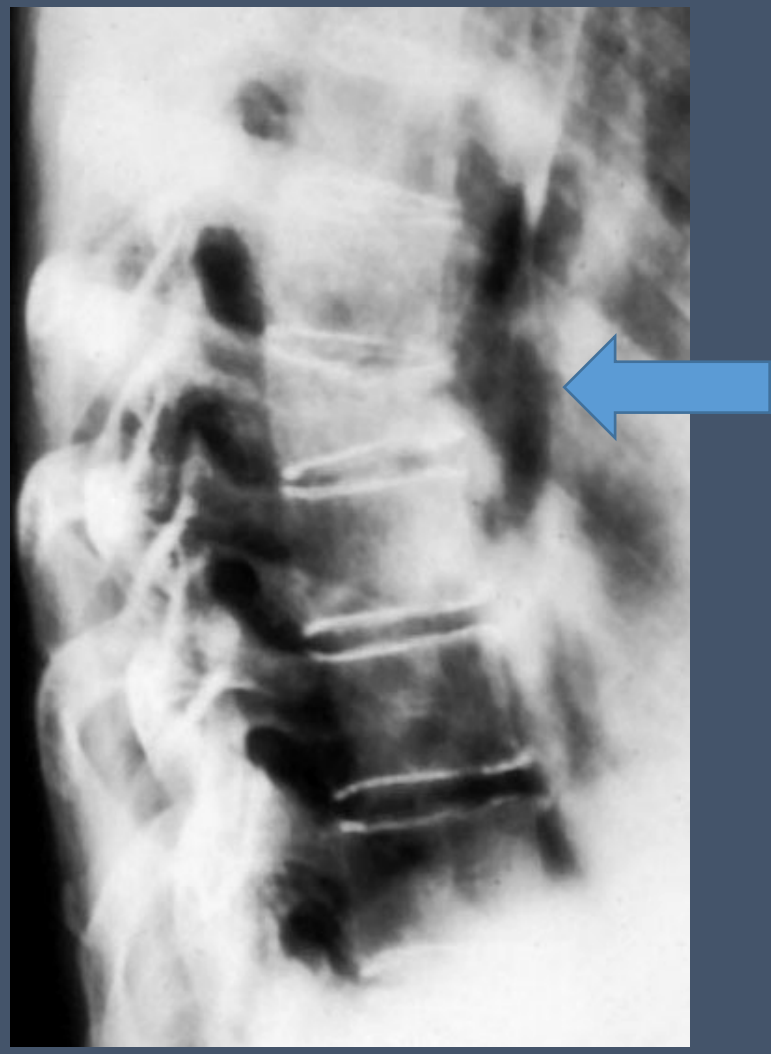


NOF Guidelines 2008 and 2010

Your Monday Morning Patient

- A 65 yo healthy postmenopausal women
- No history of low trauma fractures
- Takes 2,000 IU Vitamin D/day and a total of 1,200 mg daily calcium (600 mg/day via supplements)
- Exercises daily and does balance training
- No family history of osteoporosis
- Physical examination unremarkable but her measured height is 2” lower than her recalled maximum height at age 20 years (with a T-score of -1.2).
- What next?

Vertebral Fractures and Height Measurement



The Single Greatest Practice Opportunity ?

Detection of asymptomatic vertebral compression fractures

Asymptomatic Vertebral Compression Fractures

- 1. Represent 2/3 of VCF
- 2. In the absence of known trauma or the “dating” of the occurrence of VCF, represent a high risk in untreated patients for all osteoporotic vertebral and non-vertebral fractures
- 3. Increase prevalence with increasing age (70 years ~ 20% in women, 15% in men)
- 4. Acute and painful VCF merit an MRI to R/O pathological fracture
- 5. After a secondary workup, VCF merits pharmacological treatment; independent of the T-score or ICD-10 code and is “severe” osteoporosis

Kendler D et al Am J Med 2015
Miller PD J Clin Densit 2015
Miller PD Expert Opinion on Pharmacotherap 2016

Laboratory Testing for Postmenopausal Osteoporosis

- Basic
- CBC, SMA-12, TSH, 25-OH D, 24 hr urine calcium, serum phosphorus
- Looking for anemia, hypercalcemia, CKD, elevated or low total alkaline phosphatase, hypophosphatemia, hyper or hypocalciuria

- Complex:
- Celiac antibodies
- PTH
- Immunofixation
- ESR
- Bone turnover markers (CTX, PINP)
- Bone specific alkaline phosphatase
- Bone biopsy

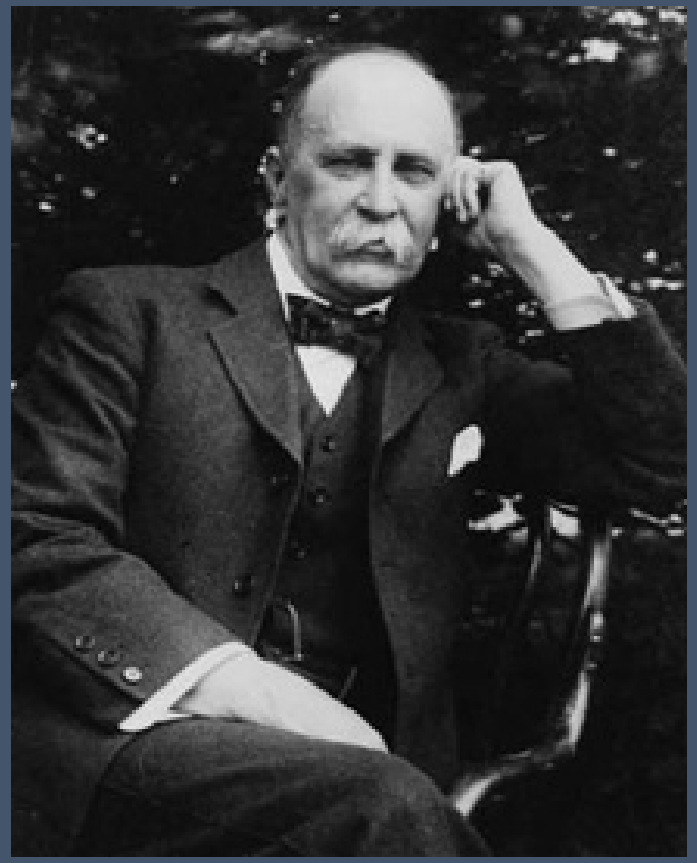
Miller PD Exp Op Pharmacother 2016

Balance for Fall Prevention: Colorado Coalition for Fall Prevention

- 1. Balance progressively declines from age 65 years forward
- 2. Falls at home and fractures are the single greatest cause of the loss of independent living from age 70+
- 3. Consistent balance program improves balance and reduces fall risk
- 4. People who work on balance in a consistent way, when they do fall, they fall safer.

Silver Sneakers; Yoga, Pilates, Tai Chi, PT…….

Treat the Person, Not Just Their Bones



"The good physician treats the disease; the great physician treats the patient who has the disease."

Sir William Osler

Osteoporosis

- 1. Prevalence increasing as we age
- 2. BMD and Bone Quality are important in defining bone strength
- 3. Secondary etiologies are common (celiac, hyperparathyroidism,etc)
- 4. Risk prediction refined by better understanding of risk factors
- 5. Current and new therapies offer choices

Thank You

Colorado Chapter of The ACP

For the invitation

Paul D. Miller, M.D.